To my friend
Dr. S. P. Felch
with the sincere regards
of Billy Duke.

# ALLERGY

## ASTHMA, HAY FEVER, URTICARIA

AND ALLIED MANIFESTATIONS
OF REACTION

BY

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*WITH SEVENTY-FIVE ILLUSTRATIONS*

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TO

PROFESSOR WILLIAM H. HOWELL

AND TO

PROFESSOR LAFAYETTE B. MENDEL

THIS VOLUME IS RESPECTFULLY AND GRATEFULLY DEDICATED

# PREFACE

In the preparation of this book, an effort has been made to present the subject in the simplest, briefest way compatible with clearness.

The subject is interesting theoretically and important practically. From a theoretical viewpoint, one may well marvel at the fact that a commonly eaten food, such as egg, can, to a sensitive individual, rank with the most violent poisons known to medical science. From a practical viewpoint, one surely should profit by acquaintance with a type of illness which affects in slight or marked degree about fifteen per cent of individuals. It is met with each day by physicians who have large practices. It is not only a common cause of illness, but is a rather frequent cause of severe illness and, in rare instances, even of sudden death.

Reaction may manifest itself in practically every tissue and in practically every organ, and simulate in almost any locality the effect of functional or organic disease. For this reason, the phenomenon should be known and looked for by physicians in every line of work if they wish to reduce error to a minimum.

My experience in the study of hypersensitiveness has been almost entirely clinical and is presented from a clinical point of view. The clinical portion of the book is based entirely upon practical experience extending over a period of twelve years, and is presented from the viewpoint of an internist rather than from that of a specialist on the subject. The data have been obtained entirely from cases observed in consulting medical office practice, and every case reviewed (over 500 in number) has been studied from a general medical point of view.

The entire routine shown in Fig. 1 was carried out whenever indicated. Even this was broadened to include studies in blood chemistry and metabolism when indicated. In every case the minimum routine included a careful and complete general medical history and physical examination, urinanalysis, examination of a blood smear, a quantitative Wassermann test, and radiographs of the teeth, according to the outline illustrated. Radiographs of the

nasal sinuses, chest, and other regions, and additional laboratory examinations were made whenever there was any clinical evidence of disease to indicate their usefulness. Finally, routine skin tests were made in every medical case if the possibility of hypersensitiveness was suggested, either by family history, personal history, physical examination, or special tests.

For specific testing, a much more elaborate routine was carried out than would seem necessary for the routine diagnosis of a case. This was done not because of the fact that it was necessary in every instance but because of the fact that in order to obtain knowledge of the value and reliability of tests with a given substance, tests with a large variety of substances have to be made for comparison. This broad use of tests with a large number of substances (at times over three hundred in number) was made possible and practical through the use of group tests,—that is, through the use of mixtures containing several different extracts. It is admitted that the data which might have been obtained routinely from individual tests with three hundred different solutions would have been more desirable. Such could not have been carried out practically, however, upon either private or charity cases. Through the use of group tests, information was often obtained which proved useful both to patient and physician, and which could hardly have been obtained in a reasonable length of time by any other method. Tests made in this way have given me a totally different impression from that held in former years when a few individual tests alone were made. While group tests were used freely, individual tests were also used in every case in which it was believed they might prove useful.

Some of the case reports which follow may seem unnecessarily long. They are printed in small type, however, so that they can be skipped by those who are not especially interested in the phase of the subject which they illustrate. Detailed complete reports are made only when indicated for the purpose of proving a point. Cases cited for the purpose of illustrating points which are in harmony with facts already known, are reported as briefly as possible.

In Part II of this book, a new group of cases is described, namely, those specifically hypersensitive to the action of physical agents, such as light, heat, cold, mechanical irritation, freezing, and burns, and in the case of heat sensitiveness, indirectly to the effect of

mental or physical exertion. This group of cases is reported in a separate part of the book because of uncertainty as to the exact nature of the pathologic mechanism responsible for reaction. I frankly believe that the mechanism is closely related to that which gives rise to sensitiveness to material agents. The data upon which this view is based are given in detail in the text and in the case reports.

Patients sensitive to the action of physical agents fall into two distinct groups which, for convenience, are described under the terms "contact cases" and "reflex-like cases." The two groups are very different clinically but seem to be related pathologically. Each group is important both from a theoretical and practical point of view. They are important from a theoretical viewpoint because it seems so strange that under certain pathologic conditions a patient may be made violently ill or even shocked by the action of a physical agent which, to a normal individual, may be absolutely harmless—in fact, beneficial. They are important from a practical viewpoint because the illnesses caused by this type of sensitiveness are both common and severe.

Since my experience with the subject of allergy has been almost entirely clinical, I have confined my own views to the clinical phases of the subject, and have borrowed the information presented on the experimental side, and on serum sickness (Chapters II to V inclusive), almost entirely from other writers, chiefly from the splendid recent textbook of Zinsser, "Infection and Resistance," and from Coca's survey, published in Tices "Practice of Medicine." From these writings especially I have quoted extensively. Readers who are interested in this phase of the subject I would refer to original sources rather than to the brief review which they will find here.

To the readers who may believe that the chapters which follow seem strange, sensational, complex, or obscure, I may say that few subjects known to medicine seem stranger. This, however, should not lead one to question the truthfulness of the facts, most of which have been proved beyond the shadow of a doubt. After all, the subject could hardly appear more strange than studies in bacteriology or immunity must have seemed in the early days of their development. So far as complexity and obscurity are concerned—every new subject must necessarily seem complex and obscure. As

carefully obtained facts accumulate, however, it should become simple—in fact, as simple as other subjects with which the profession generally is now familiar and which are accepted generally as proved and real.

In specific hypersensitiveness, we have a subject which deals with illnesses caused by inert matter. It is nevertheless as broad and may prove as important as the illnesses caused by living matter, that is, bacteria. Time alone will tell and place the subject where it belongs in the theory and practice of medicine.

In conclusion, I wish to gratefully acknowledge the kind assistance of my associates in this work, especially Mr. O. C. Durham who interested himself in the botanical side of the study, and whose work and enthusiasm has made possible a broad study of pollen in this relationship; to Mr. B. F. Bush for his help in the identification of the commoner weeds of this district; to my friend and assistant, Dr. D. D. Stofer, for his energetic work on the clinical side; to Miss Pauline DeLisse, and Miss Catherine Sweet, technical assistants, whose careful and enthusiastic work has made possible the broad use of carefully prepared solutions for testing and for therapeutic purposes; to Mrs. Clittie Stevens, roentgenologist, for her assistance in this line; to Miss Marguerite Lasley, for her assistance in recording results; and to my wife, Frances T. Duke, for her help in preparing the bibliography.

W. W. Duke.

# CONTENTS

CHAPTER XIII



CHAPTER XIV



CHAPTER XV



CHAPTER XVI

## PART II

REACTIONS CAUSED SPECIFICALLY BY ACTION OF PHYSICAL AGENTS, SUCH AS LIGHT, HEAT, COLD, MECHANICAL IRRITATION, FREEZING, AND BURNS, AND IN THE CASE OF HEAT SENSITIVENESS, INDIRECTLY BY THE EFFECT OF MENTAL OR PHYSICAL EFFORT.

### CHAPTER XVII



### CHAPTER XVIII



### CHAPTER XIX



### CHAPTER XX

# LIST OF ILLUSTRATIONS

# ALLERGY

## CHAPTER I

### INTRODUCTION

A relatively large proportion of individuals become hypersensitive to one or more foreign agents. Once sensitive, they are likely to react and display a variety of symptoms whenever they come into intimate contact with the agent to which they are hypersensitive. Through the mechanism responsible for this phenomenon a large number of harmless substances, even the ordinary foodstuffs, can come to rank in pathogenicity with the most violent poisons known. Sensitive patients coming in contact with such substances are, of course, made ill. The resulting illnesses vary from conditions which are more or less trivial to violent shock which can result fatally within a matter of seconds or minutes rather than hours. A relatively large number of the cases of sudden inexplainable death of apparently healthy individuals is due, I believe, to this condition. Dr. D. R. Newman, of Ft. Scott, Kansas, related to me the case of a child who during perfect health had a violent illness which terminated fatally within one minute after she was stung by a wasp. To a sensitive individual a relatively harmless insect may prove more dangerous than the most venomous reptile.

In the earlier years of the development of our knowledge of this subject, "anaphylaxis" was looked upon by the profession at large as an interesting laboratory phenomenon responsible at most for an occasional death following the use of therapeutic sera. As a result of two decades of intensive study by a large number of investigators, facts have been disclosed which show a condition in human beings very similar to anaphylaxis is a common cause of illness. It afflicts, in slight or marked degree, possibly as many as fifteen per cent of individuals.

Individuals can apparently become hypersensitive directly or indirectly to the effect of almost any alien agent, including foods.

drugs, pollen, hair, feathers, smoke, vapors, volatile oils, sera, insects, etc., and even, as will be shown in Part II of this volume, to the specific effect of a physical agent such as light, heat, cold, mechanical irritation, freezing, or burns and in the case of heat sensitiveness to the effect of mental or physical exertion.

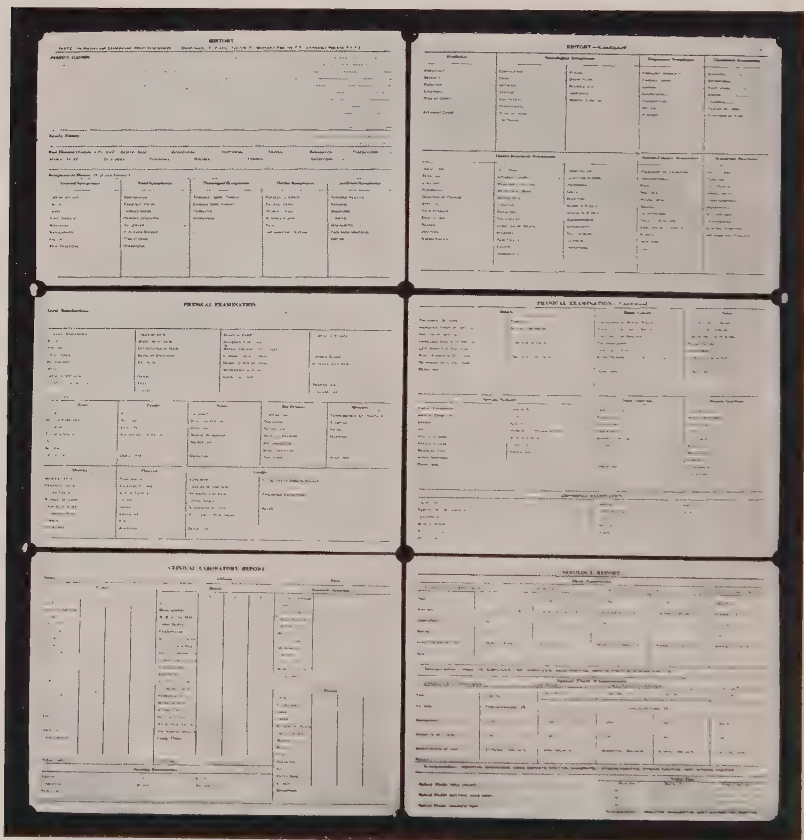

Chart I

Charts I and II.—Outline of the history and examination made in the study of the cases upon which the subject matter in this book is based. This outline is not shown because of any merit which it might possess but to show that the work upon which our study is based was thorough and complete.

The symptoms produced depend largely upon the degree of sensitiveness of the patient, the mode of contact with the offending agent, and the dose encountered. Dependent upon this, symptoms

vary in intensity, chronicity, and in location. Frequently symptoms are chiefly local, affecting tissues over very limited areas. Frequently they are very widespread, affecting almost every active tissue in the body. Because of these facts, the apparent manifestations vary greatly and may simulate other diseases in almost any locality and in almost any degree of severity. For this reason, the

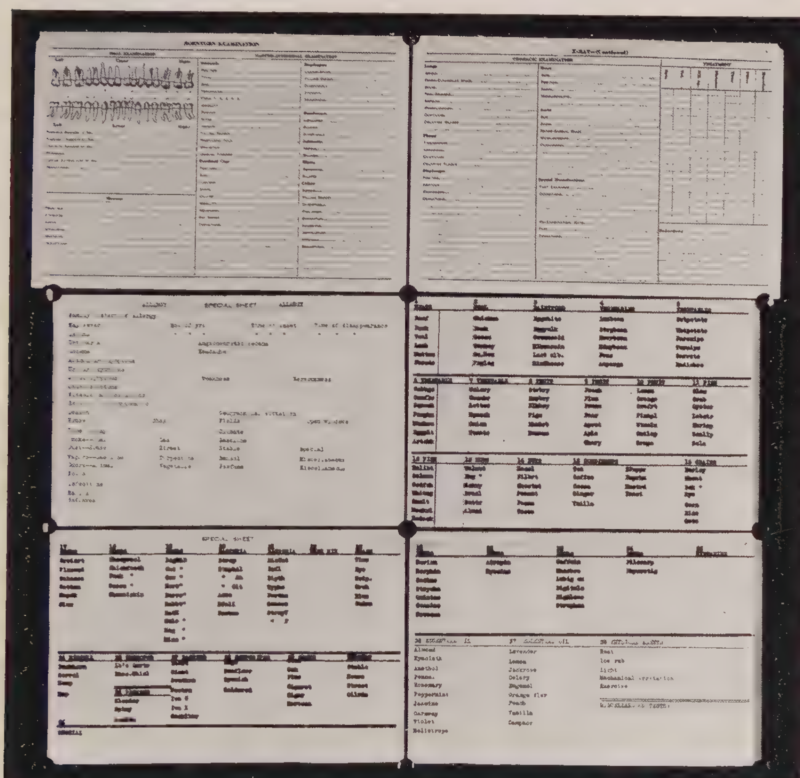

Chart II

phenomenon has to be taken into consideration by specialists in almost every line.

Several terms, "anaphylaxis" (Richet), "serum sickness," "allergy" (von Pirquet), "protein sensitization" (Vaughan), "specific hypersensitiveness" and "atopy" (Coca) have been used more or less synonymously in discussing the clinical phases of this phenomenon. Recent developments make it seem rather probable that sev-

eral different types of reaction and possibly several different phenomena have been discussed under one and the same of these terms. Furthermore, that one and the same phenomenon has been discussed under each of the several terms. This is admittedly undesirable but is not unusual in the early development of any line of knowledge. Few definitions and few classifications introduced early hormonize with later developments.

While one must admit that here, as elsewhere, a detailed classification with narrowed definitions and restricted use of terms would be most desirable, one must admit also the almost insurmountable difficulties which now face the conscientious investigators who attempt it. The differences of opinion which now exist between careful observers surely indicate that a classification which can fill all requirements is in the present state of our knowledge difficult of accomplishment.

Upon the boundaries of two terms most writers agree, namely, anaphylaxis and allergy. Doerr, Coca, Wells, Zinsser, and others all urge that the term "anaphylaxis" be restricted to proved antigen antibody reactions and that the term "allergy" be used broadly to include anaphylaxis as well as reactions of altered reactivity in which an antigen antibody reaction has not been demonstrated. Zinsser states, however, that many of the apparent differences between animal anaphylaxis and some of the reactions classed as human allergy are more apparent than real and that certain deep underlying processes may bind all these phenomena of specific hypersensitiveness together. Koessler, on the basis of recent experiments, has drawn the same conclusion. Coca has discontinued his use of the term "allergy" contending that under its heading Doerr and others have included phenomena which are not related.

"Allergy" as used by Doerr is a broad term. As stated to me by Coca, it could be used even in discussing the relationship between creditor and debtor and that cure for allergy of the sort would depend upon payment of the debt. Wells and others contend that "allergy" is a broad useful term, for under its heading can be described a group of peculiar phenomena of altered reactivity the underlying cause of which is as yet unproved. It is in this sense that I wish to use the term and it is for this reason that I have used it rather freely in discussing human cases in preference to terms such as "anaphylaxis" or "protein sensitization," and to the

term "atopy" each of which seems to commit one to a theory. I could not, for example, in the present state of our knowledge, describe "physical allergy" (altered reactivity caused by specific hypersensitiveness to the action of physical agents) under such restricted terms as "anaphylaxis," "protein sensitization," or "atopy" even though I might believe that all four conditions are remotely or closely related. Surely there can be little objection to its description under the broader term "physical allergy."

There are few illnesses more mysterious and elusive than allergy, both as to cause and cure. Yet, many writers of unquestionable ability have at various times mentioned causes and cures which they claimed would apply to almost any case. This is difficult to explain for the causes of allergy are most certainly multitudinous and upon the cause depends the effectiveness of a cure. There are few conditions met with in the practice of medicine more varied as to cause, symptomatology or cure and few which require more painstaking study if a majority of the cases, either mild or severe, are to be correctly diagnosed and then partly or completely relieved.

# PART I

## A DISCUSSION OF EXPERIMENTAL ANAPHYLAXIS, SERUM SICKNESS, BACTERIAL ALLERGY, AND ILLNESSES IN HUMAN BEINGS TRACEABLE TO SPECIFIC HYPERSENSITIVENESS TO MATERIAL AGENTS

## CHAPTER II

# EXPERIMENTAL ANAPHYLAXIS

### (Early Development)

Our knowledge of anaphylaxis has been developed almost entirely during the past two decades, although several observations which harmonize with views of present day were recorded earlier. Magendie, in 1839, observed that dogs which had been repeatedly injected with egg albumen often died suddenly. Flexner, in 1894, stated that animals which withstood one dose of dog serum would succumb to a second dose if given after a lapse of some days or weeks, even though the second dose was sublethal for control animals.

The first extended study of the problem was made by Richet, who, in collaboration with Hericourt and with Portier observed that animals which had been inoculated with eel serum or with a toxin extracted from actinae (both toxic in themselves) became unusually sensitive to their action so that second doses too small to be harmful to normal animals caused certain violent symptoms and death in animals which had been previously inoculated. To this peculiar condition Richet gave the name "anaphylaxis."

Arthus, in 1903, found that repeated subcutaneous injections of horse serum in rabbits at intervals of several days eventually gave rise to edema, sterile abscesses, and even gangrene at the site of the inoculations (Arthus Phenomenon). He found also that intravenous inoculations in the treated animals caused death. He recognized that horse serum, even when injected in large doses into normal animals, was harmless and suggested that the unusual effect of repeated doses was analogous to the condition observed by Richet, and spoke of it as "anaphylaxis."

Theobold Smith communicated to Ehrlich in 1904 the fact that he had observed that guinea pigs inoculated with horse serum for the purpose of standardizing diphtheria antitoxin acquired hypersusceptibility to subsequent inoculations given several days or weeks later. These observations were studied further by Otto, who

in 1905 described this condition as "Das Theobald Smitsche Phaenomen." He attributed the toxicity of second inoculations to the effect of the serum itself rather than to its content in antitoxin.

At about the same time the phenomenon was studied clinically by Pirquet and Schick, who described a syndrome of symptoms which occurred frequently in children seven to twelve days after an injection of therapeutic serum. This condition was designated "serum sickness." They found further that in children who were injected with serum for a second time the period of incubation was shortened so that symptoms might make their appearance almost immediately after the injection. Furthermore they observed that after second doses symptoms occurred with greater regularity and under the influence of smaller quantities of serum.

A remarkably complete series of observations were made by Rosenau and Anderson in 1906 and 1907. They first established the fact that single doses of horse serum which were harmless to normal guinea pigs made them hypersensitive so that second injections after an interval of ten days were likely to prove fatal. Furthermore that the first or sensitizing dose need not be greater than .004 c.c. for guinea pigs and that in one case sensitiveness was induced by 0.000001 c.c. of serum. Furthermore, that the condition of hypersensitiveness once established was lasting, and finally, that the hypersensitive state was transmitted from mother to offspring so that the young of treated mothers were hypersusceptible to a first injection of horse serum. They found also that sensitiveness could be induced not only by animal and vegetable proteins but also by extracts of bacteria and thought that this indicated a possible relationship between anaphylaxis and infectious diseases.

## Passive Transfer of Sensitiveness

The next step of fundamental importance was the discovery of the fact that the sensitive state could be passively transferred from sensitized to normal animals by inoculations of serum from sensitized animals. The elaboration of this fact was due largely to the researches of Doerr and Russ, although it had been demonstrated in the earlier experiments of Nicolle, Richet, Otto, Besredka, and others. Hypersensitiveness to a given antigen can be passively transferred not only by the serum of an actively sensitized animal but also by the serum of an animal in a state of desensitization or

antianaphylaxis and even by the serum of an animal born congenitally sensitive (Doerr and Russ). Transmission of sensitiveness from mother to offspring is analogous apparently to passive transfer from actively sensitized animals and depends, apparently, upon the transfer of preformed antibodies. Congenital anaphylaxis of this type, according to Coca, Wells and others, should be distinguished from inherited hypersensitiveness in human beings, to be discussed subsequently. In animal anaphylaxis inheritance comes only from the mother, and mother and offspring always have the same sensitiveness. In the case of hypersensitiveness in human beings, however, inheritance is as likely to come through the father as through the mother. Furthermore, mother and child are usually sensitive to totally different agents. Sensitiveness in animals which has been transferred passively from other animals or sensitiveness which has been transmitted from mother to offspring differs from sensitiveness actively produced by serum injections in that it is not so lasting. Sensitiveness acquired passively in either way rarely lasts more than a few weeks.

## Antianaphylaxis

The final fundamental discovery which brings us to a more detailed discussion of the present status of the subject concerns desensitization. Sensitive animals treated with sublethal doses of serum become refractory for a time so that further inoculations given during this period are harmless. This remarkable condition mentioned in the early writings of Rosenau and Anderson, Otto, and Gay and Southard, and others, was studied in great detail by Besredka and his collaborators who spoke of it as antianaphylaxis. It was found that sublethal doses of serum would not only desensitize a sensitive animal but would do so within a period of two hours or less; in fact, through the use of infinitesimal doses given intravenously at ten-minute intervals and increased rapidly Besredka rapidly conferred a degree of tolerance upon sensitized animals which would enable them to withstand from one hundred to one thousand times a lethal dose. This condition of antianaphylaxis can be established so rapidly that when a lethal dose of serum is given subcutaneously, or even when a lethal dose is given intravenously with great slowness (Mita) the animal is often de-

sensitized before the entire dose gains entry to the circulation, and in this way it is enabled to tolerate the entire lethal dose.

The state of antianaphylaxis (or desensitization) unfortunately is not lasting. Sensitiveness often returns within a period of two or three weeks (Scott). This may be traceable to new antibody production brought out partly at least by the desensitizing dose.

### Summary

Here we have knowledge of a remarkable new type of hypersusceptibility and immunity which was worked out in relative completeness within a period of a few years, the salient features of which are the following:

*First.* Certain animals inoculated with foreign protein become sensitive to it so that subsequent inoculations given after an appropriate interval are likely to prove rapidly fatal.

*Second.* The sensitizing injection is effective even when given in almost infinitesimal quantity. This, however, is not true of the shock dose which must be material in amount.

*Third.* The condition of hypersensitiveness once actively developed lasts for months or years.

*Fourth.* Sensitiveness is specific for the protein which brings the condition about.

*Fifth.* The condition can be transmitted from sensitized to normal animals by injections of serum from sensitized animals.

*Sixth.* The condition is transmitted from mother to offspring so that a first dose of serum may prove fatal to the young of sensitive mothers.

*Seventh.* Sensitiveness which is inherited or passively produced is not lasting and usually disappears within a few weeks.

*Eighth.* Animals can be made refractory quickly by treatment with sublethal doses of the serum to which they are sensitive, and can be made to withstand, without symptoms, much more than a lethal dose.

*Ninth.* The state of desensitization or antianaphylaxis is not lasting and often disappears within a few weeks.

# CHAPTER III

## EXPERIMENTAL ANAPHYLAXIS

(Later Developments)

### Characteristics of Antigens

It is very generally believed by our best authorities that anaphylaxis is a result of an antigen antibody reaction. For this reason animals can be sensitized only with antigenic substances, that is, with proteins. Animal anaphylaxis differs in this respect from hypersensitiveness in human beings in that human beings can apparently become sensitive to almost any foreign agent, both protein and nonprotein and, as I shall show subsequently, even to the action of physical agents. A statement the converse of this is true as a general rule, namely: every antigenic substance (nearly every protein) is capable of sensitizing animals. An exception is gelatine which, according to Starin has no antigenic value because of its deficiency in tryptophan and tryosine and its low content in phenylalanine. Proteins which are racemized—that is, so changed in structure that they are no longer sensitive to enzyme action are not antigenic and do not sensitize.

### Specificity of Sensitiveness

Specificity is a striking characteristic of sensitiveness to foreign proteins. Animals sensitive to one protein may not react to other proteins, even other proteins taken from the same animal or even different proteins taken from the same specimen of serum. This was emphasized by Rosenau and Anderson, who in their early work found that guinea pigs could be sensitized at the same time to several proteins, such as blood serum, egg white, and milk, and could be made to react separately and specifically to each one upon second injections. Dale and Hartley found through using the euglobulin and albumin fractions of horse serum together that each sensitized separately so that second inoculations with each would cause reaction. Wells and Osborne have obtained similar results

through using the different proteins of egg and of some of the plants.

Doerr pointed out a fact which may have an important bearing upon human sensitiveness, especially that caused by physical agents, to be described subsequently, namely; relatively slight changes in the structure of the protein molecule can change or mask its specific action. He states that a protein antigen can be altered so as to produce several substances each with individual specificity. Proteins can be altered in their specificity by iodization and by the introduction of nitro groups. According to the results of Landstiner the chemical group which is introduced determines the specificity of the protein. As suggested by Wolff Eisner this may prove interesting in relationship to drug idiosyncrasies in human beings, that is, drug idiosyncrasy may be a result of sensitiveness to a protein altered *in vivo* by a drug.

The different proteins of a given species are not necessarily related immunologically. Very frequently homologous proteins in different species of plants and animals are more alike from this point of view than the different proteins of the same species. Kraus, Doerr, and Sohma demonstrated that animals sensitized with proteins of the crystalline lens were susceptible to lens protein generally, that is, to lens protein of the same or different species of animals. Animals sensitized with lens protein, however, were not affected by serum of the same species. In harmony with this Wells and Osborne find that certain storage proteins of seeds of different species are more closely related than different proteins of the same plant.

## Site of Reaction

Important both from a theoretical and practical standpoint is the site at which the union between antigen and antibody occurs. Earlier writers were inclined to believe that it took place in the circulating blood. Later writers, however, believe that it takes place in the tissue cells. The latter view was based by Freedburger and other earlier observers, on the fact that a time interval of hours is required for the development of sensitiveness in normal animals after an injection of serum from actively sensitized animals. Sensitiveness develops to a maximum after a period of twenty-four to forty-eight hours after subcutaneous or intraperitoneal injec-

tions according to Doerr and Russ and a minimum interval of four hours is required even after intravenous injections. This time interval, they presumed, is required for the attachment of the antibodies of the injected serum to the tissue cells. Shock, they assumed is the result of union between antigen and the immune bodies which have become attached.

Other interesting observations which tend to confirm this theory are as follows:

Doerr found that as sensitiveness develops in animals treated with immune serum the anaphylactic antibody content of serum is reduced. Manwaring removed blood in actively sensitized animals and replaced it almost *in toto* with normal blood free of antibodies. These animals remained as sensitive as those which had not been bled and transfused. Pearce and Isenbrey, Coca and others, through transfusion experiments have obtained similar results. Schultz and later Dale found that smooth muscle removed from sensitized animals and washed free of serum would react vigorously when brought in contact with suitable antigens. These results and others justify, it seems, a concise statement by Zinsser which is as follows: "There is an incontrovertible mass of evidence available which proves without question that the site of the reaction which carries in its train the symptoms which we speak of as anaphylaxis, is predominantly on the cells of the body. Whether or not the intravascular reaction of antigen and antibody, which unquestionably to a certain extent takes place, has any, if even a minor importance we will discuss directly."

Given the fact that a chemical union responsible for anaphylaxis occurs chiefly in the tissue cells, the question which next arises is what cells are chiefly involved. The most constant reaction and the one which is commonly responsible for the fatal issue in animals is contraction of nonstriated muscle. In the guinea pig this occurs predominantly in the bronchioles, in rabbits chiefly in the pulmonary vessels, and in dogs chiefly in the hepatic circulation. Although this appears to be the most striking site of reaction, other tissues are also involved—in fact, the reaction is apparently widespread. Not only is nonstriated muscle in general affected, but also the circulatory system, including the blood and lymph, the secreting tissues, nervous system, etc. Because of the involvement of the nerv-

ous system the action of many organs is affected indirectly through this medium.

The chief point of attack seems to be the end organ itself or a point between the nerve ending and the end organ. This is evidenced by the fact that strips of nonstriated muscle obtained from sensitized animals contract when placed in solutions containing an appropriate antigen. However, anaphylaxis can affect many different tissues including nerve cells and influence distant tissues indirectly. Reactions produced indirectly in this way make difficult the interpretation of some of the symptoms observed in animals.

### Precipitins, Anaphylatoxins, Protein Split Products, and Hystamine

Based upon the facts at hand the majority of observers believe that the anaphylaxis reaction is a direct result of antigen antibody union and furthermore, from the site of the injurious part of the reaction lies within the tissue cells. Coca and others are even more specific and look upon it as a precipitin reaction and exclude human sensitiveness from this category because of the absence of demonstrable precipitins in the serum of sensitive persons.

A number of the earlier workers believed that with contact between antigen and homologous immune serum a combination takes place with the formation of a new body (anaphylatoxin) which in itself is poisonous and which will, upon injection into normal animals, produce the anaphylaxis reaction. Many experiments could be cited in favor of this theory and even at the present day it has a number of adherents. The anaphylatoxin theory is based upon experiments such as those performed by Richet who, in 1909, found that crepitin mixed with immune serum was immediately poisonous when injected into normal animals, even when a dose of crepitin used was in itself sublethal. Weill-Hallie and Lamaire, had previously produced typical anaphylaxis in guinea pigs by simultaneous injections of antigen and immune serum. Friedmann, Biedel and Kraus, Briot and others obtained similar results. Zinsser states that in an effort to confirm this work he occasionally obtained unmistakable severe anaphylaxis-like symptoms in rabbits, shortly after a simultaneous injection of antigen and immune serum. These results, however, were by no means constant and he could never be sure of successfully duplicating a positive result. He believes

that the preponderance of evidence points to the necessity of a time interval between injection and reaction (usually four hours or more). This, of course, would give time for the attachment of antibodies to the tissue cells and for the antigen antibody reaction previously mentioned to take place. Results of this sort, therefore, could not be used in proof of the existence of anaphylatoxins.

Interesting indeed are the early observations of Vaughan and Wheeler who split egg albumen and other food proteins and also many varieties of bacterial proteins into two fractions by digestion with sodium alcoholate. The alcohol soluble fraction, regardless of its source, was poisonous to normal animals. Whether derived from egg albumen or tubercle bacilli or other bacteria, it produced symptoms resembling anaphylaxis. The poisonous body was nonprotein and did not sensitize animals. The alcohol insoluble portion, on the other hand, was not toxic, did give positive reactions for protein, and did sensitize animals, even when given in the minute doses. Based upon these interesting results, Vaughan and Wheeler suggested that proteins introduced parentally into animals for the first time are split up slowly and harmlessly by enzymes. The effect of this injection leads to the development of a larger quantity of specific enzymes which are capable of splitting protein rapidly so that second or later injections of a given protein are likely to be followed by a quick liberation of toxic products with the production of anaphylaxis-like symptoms. These products, they considered analogous to alcohol soluble portion of their split protein. Attractive and ingenious as this theory may be one obstacle stands in the way of its hasty acceptance, namely, the time interval. The almost immediate onset of symptoms which follows the injection of sensitive animals does not fit well with a lytic process for lytic processes are usually slow. The time interval seems too short for marked protein cleavage to take place through the action of enzymes. Vaughan's views, however, cannot be discarded, especially in the case of the slower reactions and has to be taken into consideration in the discussion of reactivity in humans.

Eustis believing that toxic products absorbed from the intestinal tract played a part in the etiology of asthma, stated in 1909 that he believed such products acted similarly to muscarin. Brodie and Dixon had previously shown that muscarin is capable of producing violent bronchial contraction. On the basis of experiments described

in 1912, Eustis came to the conclusion that the Charcot-Leyden crystals found in asthma contained amines similar to cadaverine and putrescine and were a result of the putrifaction of proteins. He found that Barger and Dale had previously isolated an active principle from ergot which they identified as histamine and which upon injection into guinea pigs, cats, or rabbits would stimulate contraction of nonstriated muscles, such as of the uterus and bronchioles. Dale and Laidlaw in 1910 and later carried on extensive experiments, proving that histamine upon injection into guinea pigs gave rise to symptoms almost identical with those observed in anaphylaxis. Ackermann in 1910 found that histamine was a putrifactive product derived from histidine. In view of the fact, as Wells point out, that histidine is present in every normal protein there is a constant abundant supply of histidine free in the alimentary tract, which upon putrifaction could liberate a considerable amount of histamine. According to Koessler, the normal colon contains a lethal dose of histamine and explains the freedom from illness of the normal individual by assuming that the normal mucous membrane of the colon does not permit its absorption. The fact that histamine can produce anaphylaxis-like symptoms in animals and as found by Eustis can produce hives if applied to the skin in dilute solution, lends color to a view that the absorption of histamine-like bodies in patients with pathology in the alimentary tract might product anaphylaxis-like symptoms. It seems quite possible that this takes place in a certain proportion of human cases. The fact that it is responsible, however, for animal anaphylaxis caused by the injection of sensitive animals seems less plausible than a view that symptoms occur as a result of an antigen antibody reaction taking place chiefly in the tissue cells.

# CHAPTER IV

## EXPERIMENTAL ANAPHYLAXIS (CONTINUED)

### Symptoms

Symptoms of anaphylaxis vary in different species of animals and also vary according to the degree of sensitiveness of the animal, the dose of antigen administered and the mode of administration. Symptoms may be so mild as not to be discernible; on the other hand, they may be so severe as to terminate fatally within a few moments. Many of the milder symptoms are no doubt not demonstrable in animals by our present methods of study so that the summary quoted from Zinsser's recent textbook, which follows, refers chiefly to the more striking symptoms.

### Symptoms of Anaphylactic Shock. Quoted from Zinsser

"If a properly sensitized guinea pig receives a second injection of an antigen after a suitable incubation time a very characteristic train of symptoms ensues. There is usually a short preliminary period—lasting either a fraction of a minute or several minutes according to the violence of the reaction and the mode of administration—during which the pig appears normal. At the end of this time the animal will grow restless and uneasy, and will usually rub its nose with its forepaws. It may sneeze and occasionally emit short coughing sounds. At the same time an increased rapidity of respiration is noticeable and the fur will appear ruffled. In light cases the animals may remain in this condition, with further irregularity and difficulty of respiration, possible discharges of urine and feces; then gradually slow recovery may set in, with complete return to normal in from thirty minutes to several hours. In more severe cases these preliminary stages are rapidly followed by great apparent weakness. The animals fall to the side, the legs and trunk muscles twitch irregularly, and the respiration becomes slow and shallow; the thorax never entirely contracts, but remains in a more or less expanded condition. The very evident dyspnea is of an inspiratory character. The excursions of the lung itself seem to grow shallower and shallower in spite of apparent strong inspiratory efforts—the volume of the thorax and lung remaining in the expanded condition. At this stage evidences of motor irritation may appear, in that the animal may arise and attempt to run. More often, however, in this phase general convulsions set in, often several times repeated, and in these the animals usually die.

"On the other hand, after cessation of convulsions they may lie perfectly still on the side as though paralyzed, the breathing becoming gradually slower and more shallow, finally ceasing entirely. The heart may continue to beat for a considerable time after the breathing has stopped.

"If such an animal is immediately autopsied a very characteristic condition is found—to which, in the essentials, attention was first called by Gay and Southard. They speak of finding 'pulmonary emphysema as a constant feature at autopsy,' and attribute the anaphylactic death in guinea pigs to cessation of respiration in the inspiratory phase under the influence of respiratory central intoxication.

"The lungs of such guinea pigs after death are found distended and completely filling the thorax. They are usually pale and bloodless and do not collapse as the pleurae are opened. On microscopic examination the alveoli are seen to be distended and small hemorrhages may appear upon the serous surfaces. According to Gay and Southard, furthermore, histological study of the other organs shows also hemorrhages in the brain, stomach, heart, cecum, and spleen—more rarely in other organs—and there are local fatty changes in the capillary endothelium which they regard as causatively related to the hemorrhages.

"That the respiratory symptoms are the most striking feature of the clinical picture of guinea pig anaphylaxis had, as a matter of fact, been noticed by Rosenau and Anderson. A detailed physiological study of the mechanism of the respiratory death in these cases was first made, however, by Auer and Lewis in 1909.

"These investigators showed that, during the later respiratory symptoms, little or no air enters the lungs, although the animal makes violent respiratory efforts. This is due, as they found, to a tetanic contraction of the small bronchioles, which practically occludes the air passages. That the origin of this contraction is not, as previously supposed, of central origin, but is referable to peripheral cause, they proved by showing that the same phenomena occur in the guinea pigs even after the cord and medulla have been destroyed and the vagi divided. In such cases, of course, with the cord and medulla destroyed, artificial respiration had to be done, and when the symptoms set in it was found that the lungs could no longer be expanded by the same force of artificial respiration which before this had been sufficient.

"They showed also that the noncollapsible expansion of the lungs after death was due to imprisonment of the air in the alveoli by the contracted musculature of the small bronchioles, and further confirmed their opinion of the peripheral origin of this contraction by the important discovery that atropin will markedly protect, often preventing death or hastening recovery. It is noteworthy, too, that Auer and Lewis speak of occasionally finding slight pulmonary edema, a feature which Biedl and Kraus consider incompatible with true anaphylaxis.

"Anderson and Schultz, who have confirmed much of the work of Auer and Lewis, find that not only atropin will prevent asphyxiation in these cases, but methane, chloral hydrate, adrenalin, and pure oxygen will exert a similar effect. The animals may be saved from suffocation in this way, but may nevertheless die, probably as the result of lowered blood pressure.

"The observations of Auer and Lewis have been further confirmed especially by Biedl and Kraus, who regard it as well established that anaphylactic death in guinea pigs is caused primarily by suffocation, due to tetanic spasms of the musculature of the small bronchi. These spasms are not of central origin, but are peripherally initiated, possibly by direct action upon the smooth muscle itself. The fact that atropin is not effective in preventing death in all severe cases is no argument against this, since such an effect would naturally depend upon the relation between the amount of atropin given and the severity of the attack. In this connection the studies that have been made upon the irritability of smooth muscle fibers in normal and in sensitized animals are of great interest. Schultz, following out an observation made by Rosenau and Anderson, studied the intestinal muscle of normal sensitized guinea pigs, excised and suspended in Howell's solution. In this way he showed that during the period of hypersusceptibility the smooth muscle is abnormally sensitive to treatment with the antigen. The contraction which normally occurs in smooth muscles under the influence of serum is markedly augmented if the preparations are taken from sensitized animals.

"In addition to these predominant features of the anaphylactic symptomatology in guinea pigs, there are a number of secondary reactions which though less prominent, are nevertheless of considerable interest and theoretical importance. The conditions in the circulation are probably, to a great extent, dependent upon the respiratory condition, and the fall of blood pressure in guinea pigs is regarded by some investigators as merely a secondary manifestation just preceding death. The fall of temperature first described by H. Pfeiffer, however, seems to be an occurrence which, though standing in no causative relation to the symptoms as a whole, is so constant and well marked that it has been taken by a number of workers as one of the necessary criteria for the characterization of the anaphylactic condition.

"There is, indeed, an almost regular drop of several degrees in the rectal temperature, and a close observation of this may be of much aid in determining the occurrence of mild reactions, when other symptoms of shock are not strongly marked. Pfeiffer himself goes so far as to claim that by this symptom alone delicate anaphylactic reactions may be determined when all other symptoms are lacking.

"Friedberger, too, has found the sudden drop of temperature a very regular occurrence, and has employed this method of study for the analysis of the intensity of anaphylactic shock. He calls attention to the apparent difference between infection and anaphylaxis in this respect in that in the former there is fever, in the latter there is depression of body heat; but, at the same time, he points out that this discrepancy is an apparent one only, and determined by quantitative differences, for when he treated sensitized animals with varying doses of antigen he found that quantities which produced other anaphylactic symptoms of noticeable degree would regularly depress the temperature as Pfeiffer had shown. It was possible, however, to determine a minimal dose necessary for temperature reduction. Quantities just below this left the temperature unchanged, and still smaller quantities produced fever or even increased the temperature. This fact is extremely significant in that, as we shall see,

it has an important bearing upon views which interpret bacterial infection as a series of anaphylactic poisonings, the multiplying bacteria furnishing the constant supply of minute amounts of antigen. This thought, indeed, based also on the study of temperature curves in animals, was expressed by Vaughan as early as 1909, and was developed by him with Cumming and Wright in an extensive study upon what he called 'protein fever.' It was shown in these experiments that continued fever, not unlike that of infectious diseases, could be produced in rabbits by repeated subcutaneous injections of primarily harmless substances, such as egg white and vegetable proteins. The conditions observed and the conclusions drawn from them in this work, as well as in the similar investigations of other workers, were clearly foreseen by Vaughan in his early investigations on protein split-products studies, which we shall find occasion to discuss in a later section.

"The rigidity of the diagnostic value of the temperature relations for anaphylactic shock in particular, as advanced by Pfeiffer, was somewhat weakened by Ranzi's observations that foreign serum may produce temperature depression when injected into perfectly normal animals and that, injected into sensitized animals, the same reaction may follow if other proteins than the original antigen were administered.

"Although these objections of Ranzi are perfectly just, yet there is such a marked quantitative difference between the reaction in normal and in sensitized animals that, in principle, Pfeiffer's claim is not invalidated. Friedberger very logically remarks that, after all, the phenomena of sensitization as well as those of immunity are merely an exaggeration of normal physiologic conditions, and in experiment he has shown that, whereas noticeable depressions of temperature will follow in the normal animal only upon quantities of antigen exceeding 0.5 c.c., the temperature of the sensitized animal may be depressed by amounts as small as 0.0005 c.c.

"Apart from the symptoms so far discussed, there are other less apparent characteristics of anaphylaxis in guinea pigs, all of which, however, possess considerable importance theoretically. The most significant of these is the reduction in the amount of alexin or complement, first noticed by Sleeswijk, which occurs after the injection of the second or toxogenic dose—during the development of shock. This phenomenon is so closely interwoven with later theoretical aspects of anaphylaxis that we will defer its discussion until we have completed a more general survey of the field.

"In guinea pigs, as in dogs, Friedberger and others have also seen a lowered coagulability of the blood and a temporary diminution of the polynuclear leucocytes (leucopenia) during shock."

"**Differences Between Physiologic Reactions of Guinea Pigs and Other Animals.**—We have described the occurrences in guinea pigs at some length because protein anaphylaxis has been most thoroughly studied in these animals. We have already seen, however, that in discussing active sensitization, there are marked differences in the anaphylactic phenomena as they occur in different species of

animals. The physiologic reactions noted in guinea pigs, therefore, as a result of anaphylactic insult, cannot, indiscriminately, be applied to other animals.''

''In sensitized rabbits the injection of a further dose of antigen is usually followed, after a short but definite incubation time, by great weakness with, often, discharge of urine and feces. The animals sink down until the abdomen touches the ground, the legs are stretched out weakly but not paralyzed, and the head may drop forward or to one side. After this, the animals may gradually fall upon its side and lie motionless except for labored and irregular breathing and occasional twitching of the legs and head. Sometimes this gradual relaxation may be interrupted by a sudden motor irritation, the rabbit suddenly getting up and running a short distance but soon falling down again apparently from a sudden return of the muscular weakness. During these running spells it seems as though there was no sense of direction or purpose—the animals running into obstructions or off tables as the case may be. During this period general convulsions and a drawing back of the head by a tetanic spasm of the muscles of the neck are not uncommon. Death may occur within a few minutes, or it may follow a gradually increasing weakness in the course of several hours. The fall of blood pressure here seems to be purely secondary to the general failure of all the functions.

''Unlike guinea pigs, rabbits do not show the distention of the lungs found in guinea pigs. Characteristic, however, is the distention of the right side of the heart and, as Auer first noted, there is a definite pathologic change in the muscles of the right ventricle which he believed was directly connected with anaphylactic death. This supposition has been recently confirmed by an important observation by Coca, who perfused the vascular pulmonary system of normal rabbits and of rabbits dead of anaphylactic shock. He found that while a pressure of 10 cm. will easily perfuse the normal pulmonary vascular system of the rabbit, a similar experiment on rabbits that have just died of anaphylactic shock failed, even under a pressure of as much as 90 cm. When he cut the lung near the pleural surface in such rabbits, while this pressure was being applied, no fluid oozed through, proving that the obstruction is on the arterial side of the pulmonary circulation. He justly concludes that death in the anaphylactic rabbit is probably due to a tonic spasm of the muscular coat of the pulmonary arterioles. Coca suggests that a similar spasm in the systemic arterioles may take place in the anaphylactic rabbits, and that such a localization of the anaphylactic reaction in the arterial walls may account for the local manifestation spoken of above as the Arthus phenomenon which is peculiar to rabbits so far, and has not yet been satisfactorily explained.

''Anaphylaxis in dogs has been very extensively studied, especially by Biedl and Kraus, and by Pearce and Eisenbrey. The symptoms in dogs are characterized by a rapid progressive fall in the blood pressure, followed by the symptoms of cerebral anemia. Anaphylactic dogs, after injection, will at first grow restless, vomit, and pass urine and feces. They then grow rapidly weak, fall to the ground, and continue to twitch and vomit and the respiration becomes labored and irregular. There is general weakness of the muscles, but

no paralysis. The marked, constant, and characteristic feature of the condition in these animals is the fall of blood pressure. There is also a lessened coagulability of the blood, much more strongly developed than in guinea pigs and rabbits.

"According to Biedl and Kraus this may amount to almost a prevention of the coagulation in anaphylactic dogs.

"As in other animals the blood picture is changed in that there is a falling off of the total number of leucocytes with a relative diminution of polynuclear cells.

"Quantitative measurements by Calvary, moreover, have shown that anaphylaxis in dogs is accompanied by a marked increase of the lymph flow (seven times the amount observed in normal dogs in the same time), and, by controlling the blood pressure with barium chloride, that this lymphagogue action is not directly dependent upon the low pressure. This observation is of especial interest in connection with the similarity of anaphylaxis to peptone poisoning in which Heidenheim noticed a similar increase of the lymph.

"Pearce and Eisenbrey found, at autopsy of dogs dead of anaphylactic shock, subserous petechial hemorrhages in the rectum and gall bladder, hemorrhagic spots on the gastric and duodenal mucosa, and in the colon. According to these workers, in agreement with Biedl and Kraus, the fall of blood pressure is not due to central causes but depends upon influences exerted upon the peripheral vasomotor system. Biedl and Kraus believe that this action is exerted upon the muscle cells themselves rather than on the nerve endings. They admit the inconclusiveness of their experimental data, but take the above standpoint because of the fact that adrenalin, which acts by stimulation of the vasomotor nerve endings particularly, does not raise the low pressure in dogs during anaphylaxis while barium raises the blood pressure in such animals. Pearce and Eisenbrey are inclined to believe that the action is chiefly upon the nerve endings, though both factors, nerve and muscle, may be involved. They worked with apocodein, a substance which, in large doses, paralyzes the vasomotor nerve terminals.

"When a sensitized dog was treated with apocodein and the antigen then injected, no further drop of pressure was obtained. Apparently a paralysis of the vasomotor nerve endings had removed the point of attack upon which the anaphylactic poison could act.

"In addition to the symptoms already enumerated, Weichhardt and Schittenhelm claim that anaphylaxis in dogs is invariably accompanied by a severe local reaction in the gut. The intestinal mucosa is swollen and contains miliary hemorrhages and the lumen is often filled with a mucus mixed with blood. In the further analysis of the anaphylactic reaction in dogs, Manwaring has recently reported observations of great interest. He investigated the participation in anaphylactic shock of the various organs and determined that shock did not occur when the abdominal vessels were ligated just above the diaphragm. In further localizing the source of shock he found that exclusion of the spleen, stomach, kidneys, suprarenals, and ovaries from the circulation had no effect upon the occurrence of anaphylactic shock. However, when he operated in such a way that the liver was thrown out of circulation, none of the seven dogs

that he used reacted with anaphylactic shock to the injection of serum. He concludes from this that the liver is directly responsible in some way for the production of anaphylaxis. The intestines, too, were found, by a similar procedure, to take part, though to a less important extent than the liver.

"It would seem, in view of a number of confirmations of Manwaring's work, that the great importance of the liver in anaphylactic dogs cannot be questioned. Richard Weil, who also investigated these conditions, believed that most of the circulatory disturbances in the anaphylactic dog could be attributed to obstruction in the portal circulation.

"Recognizing as fairly well established that in the three animals most thoroughly studied in anaphylaxis, namely, the guinea pig, rabbit, and dog, physiologic reactions and localization in organs vary distinctly, many attempts have been made to explain such differences. In guinea pigs, as we have seen, the cause of death resides very largely in the musculature of the bronchioles, in rabbits a similar cause is found in the circulation of the lung, and in dogs the hepatic and splenic circulations seem to be particularly involved. A most ingenious and plausible explanation is suggested in Wells' review as the result of anatomical studies by a number of different workers. He states that histologic study of guinea pigs has shown an astonishing development of the bronchial musculature, the finer bronchioles consisting almost entirely of muscular tubes. In rabbits 'the pulmonary arteries present a remarkable degree of muscular development analogous to that of the guinea pig bronchioles.' As far as dogs are concerned, he quotes Simonds as stating that the walls of the hepatic veins of the dogs are different from those of any other animal, again, in showing a very high development of musculature. And, Wells concludes, it is at least a reasonable hypothesis that the differences in these species, in reaction to one and the same mechanism, depend upon fortuitous differences in the distribution of nonstriated muscle. Interesting in connection with Wells' suggestion, is the fact that Huber and Koessler have shown that asthmatic individuals show a hypertrophy of the musculature of the bronchioles which transforms them histologically into a condition not unlike that normally prevailing in the guinea pig, and it is well known that in such individuals severe attacks of an asthmatic nature can be elicited on serum injection. As a matter of fact, it is in individuals of this sort that one avoids or exercises unusual care in connection with protein injections.

"Other animals than those mentioned have been little used for anaphylactic experiment. Observations incidental to other work, however, have shown that horses and goats are particularly sensitive. In goats the writer has observed both serum and bacterial anaphylaxis, and the symptoms here were those of general trembling, weakness, labored respiration, and involuntary evacuation of urine.

"The lower monkeys are exceedingly difficult to sensitize. Our own experiments on this subject have already been cited. When, after repeated injection, sensitization is accomplished, the symptoms are usually mild, and not unlike those prevailing in human beings, in fact, we have cited a single case in which edema of the face and a picture somewhat similar to serum sickness in man results.

Mice can be sensitized but not so easily as guinea pigs. The best method consists in giving several relatively large preliminary doses a few days apart. Anaphylactic reactions in man will be discussed in a subsequent section.

"Rats are refractory to sensitization. Longcope's work with isolated rat uteri was entirely negative. F. and J. T. Parker in our laboratory have obtained mild uterine reactions, but so far no uterine response."

"In the discussion of the anaphylactic reaction given above, we have dealt chiefly with the very severe symptoms of acute shock. It must not be forgotten, however, that these conditions are the manifestations of a very acute and profound injury, and the localizations in various organs with which we have dealt are chiefly those which are responsible for death, perhaps to a large extent, or entirely, because these particular sites of injury affect the tissues upon which the immediate continuation of life depended. It is not at all out of question, however, that many other parts of the body may suffer, although their injury might have no immediately noticeable effects, but expresses itself, eventually, especially if the insult is repeated, in degenerations and chronic disease. Chiray and Longcope have attempted to approach this problem by repeated administrations of protein in moderate doses to rabbits and investigation or subsequent changes in the kidney. The lesions found by Longcope were interpreted by him as perhaps signifying a subacute anaphylactic injury. This conclusion, however, has been questioned, since then, by a number of workers who believe that similar lesions are too frequently found in untreated animals to permit definite assumption that the repeated protein injections had caused them. Boughton has made observations similar to those of Longcope, and though the question must remain an open one for perhaps some time to come, it is, nevertheless, reasonable to suppose that, whether or not these particular experiments of Longcope and of Boughton can be accepted as proof, the likelihood is strong that repeated anaphylactic reactions of whatever severity, may cause injury to many organs in which they cannot be immediately observed."

# CHAPTER V

## SERUM SICKNESS

A rather large proportion of individuals who have received injections of therapeutic sera present, after a period of from several hours to ten days (usually the latter), a syndrome of symptoms which von Pirquet and Schick designated as serum sickness. Although the first detailed description of the condition was given by von Pirquet and Schick, it had been previously noticed by other observers, even at as early a date as 1667 by Dennis after a transfusion of lamb's blood and in 1874 by Dallera (cited by Coca). Serum sickness differs from anaphylaxis just described in that it afflicts individuals who have not received previous sensitizing doses of serum.

The incidence of serum disease varies greatly in different localities due, no doubt, to differences in the preparation of sera used and to differences in methods of administration. Unruhe reports an incidence of only 2.2 per cent in patients receiving therapeutic sera, while Axenow, at the opposite extreme, reports 66 per cent. Extreme differences of this sort might be attributable not only to differences in the kind and quantity of serum used and in methods of administration but also to variance in opinion as to the identity of symptoms which can be classed as serum sickness.

It is generally recognized that the larger the dose of serum the more likely are symptoms of serum sickness to appear and the more severe are they likely to be. According to Weaver, only 10 per cent of individuals have serum sickness when less than 10 c.c. are used, while over 75 per cent have symptoms after the use of quantities greater than 10 c.c. With the use of antitoxin as prepared by methods such as the Adkinson-Gibson method which eliminates a large proportion of the protein the incidence of serum sickness can be still further reduced and the symptoms in the cases which do react are usually less marked than in cases where the less highly purified preparations of antitoxin are used.

Von Pirquet and Schick in their early work made the important observation that second injections of serum were more likely to

cause illness than first injections and furthermore, that following second injections symptoms were likely to appear after a shorter period of incubation and were, as a rule, much more severe. This observation is of great practical importance because if human beings, like animals, are rendered sensitive by treatment with serum, second injections should be used only in case of very grave emergency and first injections should be avoided if possible. This fact, if true, would greatly reduce the sphere of usefulness of therapeutic sera. When we consider the extent to which antitoxin has been used to reduce both the mortality and incidence of contagious diseases such as diphtheria, the facts in the case should be weighed carefully by physicians before second injections are looked upon as dangerous. The fact is, that it appears to be extremely difficult to sensitize human beings to foreign agents in the same sense that guinea pigs can be sensitized by injections of foreign sera. According to Coca and others, it seems practically impossible to sensitize a human being to such an extent that a second injection will cause true anaphylaxis—in fact, Coca fears first injections more than second injections because of the fact that if a person tolerates one dose, he is practically sure to tolerate a second dose. The first dose if tolerated reduces the likelihood of the existence of a naturally acquired idiosyncrasy against horse serum which makes the use of serum so dangerous. While first injections of therapeutic sera do actually make more likely the occurrence of serum sickness, after a second dose this fact need not interfere with the use of therapeutic sera in case the indication for its use is real, for serum sickness almost never proves fatal.

In proposing a theory in explanation of mechanism of serum sickness, von Pirquet and Schick assumed that the reaction was the result of a combination between antibody induced under the influence of the injection of serum with persisting traces of the serum in the blood. This rather logical view was based upon several facts. First, upon the long incubation period usually intervening between injection and reaction (usually eight to twelve days). This is adequate time for antibody formation. Second, upon the fact that after second doses the period of incubation is usually shortened or almost entirely lacking. This could be a result of union with antibody induced by the first dose. Finally, upon the fact that after second inoculations local edema frequently occurs about the site of

the injection. This might be a result of local reaction between preformed antibody in the tissues and body fluids and the antigen injected.

Coca draws an interesting analogy between serum sickness and the drug idiosyncrasies and objects to an assumption that either can be classed definitely as a result of antigen antibody combination. Zinsser, on the other hand, considers serum sickness more closely related to anaphylaxis than to the drug idiosyncrasies. Many who believe the remarkable similarities between the three conditions seem to overshadow the differences are inclined to attribute the differences to the variance in degree of sensitiveness and to variance in the natural tendency of certain species of animal and of certain individuals to react or not to react. The fact that symptoms appear in the absence of demonstrable antibodies seems to present no great obstacle to the acceptance of the theory of von Pirquet and Schick for few, if any, processes of immunity run consistently parallel with demonstrable bodies.

As previously mentioned, the incubation period between serum injection and onset of symptoms usually falls between eight and twelve days. This varies, however, from a few minutes to twenty-four days or more. In 32.8 per cent of Hasting's cases, the eruption appeared between ten to twelve days. These, he called the critical days. However, in 23.4 per cent symptoms appeared within the first three days. Von Pirquet and Schick, on the basis of the observation that the period of incubation after a second injection was shortened and that the incidence of symptoms was more constant and the symptoms observed more severe, suggested that the reaction capacity of the individual was altered by the first injection. Both this observation and explanation has met with the approval of other observers. They found, furthermore, that if a second injection was made during the interval in which antibodies were still present in the circulating blood (usually between the twelfth day and fifth month) the reaction was likely to occur immediately (called immediate reaction) rather than after a period of hours or several days (called accelerated reaction). The latter, or accelerated, reaction was the rule when injections were made at dates later than those above mentioned. They reported five cases in which two reactions occurred after a single injection. They considered the first an immediate reaction and the second an accelerated reaction. Double

reactions have even been observed following first injections of serum by Dout and others. Even triple reactions have been observed by Goodale and others; in one of Goodale's cases occurring on the first, third, and seventh day and in another on the second, seventh, and tenth days. Axenow reports quadruple reactions following the use of scarlet fever serum. All these reactions should be distinguished from the shock reaction which occasionally immediately follows a first injection. This can usually be blamed upon a naturally acquired sensitiveness to serum to be discussed subsequently.

## Treatment of Serum Sickness

Fortunately, the average case of serum sickness is disagreeable rather than dangerous. For this reason, therapeutic sera should almost always be used if strongly indicated but should always be used with care.

The treatment of serum sickness lies largely in prevention. It cannot be prevented, however, when large doses of serum are given, especially if given intravenously. This fact must be borne in mind in deciding whether or not indications are urgent enough to justify this method of administration.

Since serum sickness depends largely upon the amount of protein injected, the use of the smallest amount possible of the most highly purified preparation is the method of choice and, for the same reason, the subcutaneous or intramuscular method is preferable to the intravenous unless indications make the use of the latter seem urgent.

The chief danger in the use of therapeutic sera lies not in serum sickness following either first or second doses, but rather in the fact that a few individuals are naturally hypersensitive to horse serum. There are cases of the sort on record in which a fatal outcome has followed the use of 1 c.c. of serum subcutaneously and 1 minim intravenously. This type of hypersensitiveness can usually be foreseen if a careful inquiry concerning sensitiveness to horses is made and also a careful inquiry in the patient's history or in his family for allergic diseases, such as hay fever, asthma, chronic urticaria, eczema, etc. In patients giving a positive personal or family history of the above symptoms the possibility of horse serum sensitiveness should be suspected and serum should be administered with unusual care and in the smallest dosage possible, and this

only after the patient has been tested intracutaneously with the injection of .01 c.c. of serum. If a wheal appears the serum should be given according to Coca's method as follows.

Unfortunately, it is difficult to desensitize in the case of natural sensitiveness to horse serum. The method used by Besredka in desensitizing animals made artificially sensitive to serum cannot be used in human beings for two reasons. First, because the degree of sensitiveness is much greater and in the second place, because the process of desensitization takes place more slowly than in animals and is much more difficult to bring about. If, in the case of proved sensitiveness to horse serum the indication is urgent enough to justify the use of serum, Coca recommends the giving of 0.1 c.c. of the therapeutic serum subcutaneously. This can be repeated and increased at thirty-minute intervals by not more than 0.1 c.c. When a point is reached at which the serum causes reaction, the dose should be reduced some and cautiously repeated at thirty-minute intervals until the desired amount of serum has been administered. This can usually be done with safety.

For symptomatic treatment, adrenalin and atropine is advised both before serum is administered and as often as is necessary after its administration. For the details concerning this, the reader is referred to a subsequent chapter.

**Symptoms.**—The symptoms of serum sickness, which appear typically in about eleven to thirteen days after the injection but which can vary in time of appearance in extreme cases from several hours to several weeks, are, according to a splendid summary by Coca, about as follows:

"**Fever**—Elevated temperature, though a frequent accompaniment of the eruption of serum disease, is not constantly associated with that symptom. In Hartung's series, it was absent in 24 per cent of the cases that presented an eruption. The degree of the fever is often considerable, reaching, in two of Hartung's cases, as high as 106°-106.5° F. The duration of the fever corresponds, in the main, with that of the eruption with, however, numerous exceptions. The highest point of the fever may be reached as early as two days before the appearance of the eruption, or as late as the eighth day of the rash. However, this climax is most common on the day of the appearance of the rash or on the day previous to its appearance. In some instances the fever is present only on the day preceding the appearance of the eruption, after which the temperature remains normal. The course of the fever is usually of remittent type, though sometimes it is intermittent.

"**Eruption**—The eruption of serum allergy is highly polymorphous, different forms often occurring at one time in the same individual. The different anatomical forms encountered are the erythematous, the intensely itching urticarial, the papular or maculopapular, the vesicular and the hemorrhagic. The chief clinical types are the scarlatiniform, the morbilliform and the so-called erythema exudativum multiforme. The serum eruption is local; that is, occurring about the site of injection, or general, involving, symmetrically, all parts of the skin surface.

"**Local Eruption**—Generally speaking, the local eruption seems to appear earlier than the general eruption. In no instance observed by Hartung did a local eruption appear later than the sixth day after the injection, and 71.4 per cent of such eruptions were present by the second day. Babinski, however, saw a local eruption appear as late as the tenth or twelfth day and in Unruhe's series most of such eruptions occurred between the seventh and the twenty-second day. According to Hartung, the local eruption is generally unaccompanied either with fever or with subjective symptoms. The local eruption is usually followed by a general eruption. However, according to von Pirquet and Schick, the general rash may be missing. A considerable interval of time may separate the appearance of the local eruption and that of the general eruption—as much as thirteen to twenty days in some cases.

"**General Eruption**—This often appears in 'crops' over several days. There is, also, a distinctly recurrent form of the general eruption, which may be separated from the first general eruption by a considerable interval of time that shows, however, no constancy (five to twenty-one days), although in Hartung's collected series a large proportion of the recurrences took place after an interval of about two weeks.

"**Mucous Membranes**—Very exceptionally the mucous membranes appear to be involved in serum allergy. The angina-like changes in the throat described by Hartung were not seen in any case by von Pirquet and Schick, and the conjunctivitis and rhinitis of Hartung could not be referred, by von Pirquet and Schick, to the serum injections. The latter authors, however, are inclined to believe that the bloody diarrhea noted in two of their cases, like the diarrhea noted in three cases by Hartung, were due, in some way, to the injection of the serum; they noted, also, elevated, reddened spots on the conjunctiva during the serum eruption in two cases.

"**Joints**—Pain and tenderness in the joints occur in serum allergy, being found in from 1 to 1.9 per cent of all injected individuals. The metacarpophalangeal joints appear to be more frequently affected than other joints. Hartung reports some cases in which swelling of the joints was a prominent accompaniment of the pain. Von Pirquet and Schick, on the other hand, state that it is just the absence of objective joint symptoms that characterizes the painful condition of the joints in serum diseases. They observed no instance of swollen joints in their series. Besides the joint pains there are sometimes observed rheumatoid pains in the muscles.

"**Edema**—This symptom of serum allergy, though previously observed, was given particular study by von Pirquet, which consists in estimating the amount of edema from the increase in body weight. These authors found that the

edema is sometimes associated with albuminuria and they pointed out the fact, which distinguishes the edema of serum disease from that of nephritis, that in the former condition, the edema appears before the albuminuria, whereas in nephritis this order of appearance is reversed. The edema of serum allergy is, thus, not of renal origin. The edema of serum disease, like that of nephritis, affects most commonly the face, especially the eyelids and also the dependent parts of the body. It disappears with the other symptoms of the condition.

The albuminuria of serum disease is always slight, according to von Pirquet and Schick not over 1/40 per cent.

"**Lymph Nodes**—Enlargement of the lymph nodes was noted in serum disease by the earlier authors, but von Pirquet and Schick ascribed to it a special importance as one of the most constant of the symptoms and, furthermore, as useful in prognosis inasmuch as it makes its appearance before any of the other symptoms and it is the first symptom to subside. The enlargement, which is accompanied by pain and tenderness, affects chiefly, and sometimes only, the regional nodes, a general adenitis, however, occasionally occurring.

"**Leucopenia**—The changes in the leucocyte content of the blood in serum disease were first studied by von Pirquet and Schick, who observed that when any noteworthy alteration did take place in this respect it was always a diminution in the total number of the leucocytes at the expense of the polynuclear cells."

## CHAPTER VI

## BACTERIAL ALLERGY

In an infectious disease lasting longer than the incubation period of ten days or more necessary for the sensitization of an animal to foreign protein, we have a condition in which we should expect symptoms resembling serum sickness—that is, a presumably sensitized individual in intimate contact with the substance which sensitized him. Rosenow and Anderson, in their earlier work, recognized this possibility and succeeded in sensitizing animals with bacterial extracts, such as B. coli, tubercle bacillus, anthrax, and typhoid bacilli and produced symptoms resembling serum anaphylaxis upon reinjecting the appropriate extract. They suggested that the incubation period for many of the infectious diseases represented the time necessary for the development of sensitiveness. Rosenow and Anderson's results were confirmed by Kraus and Doerr, Halobut, Delanoe, and more recently and more conclusively in a graphic way by Huber and Koessler. All agree, however, that it is not so easy to sensitize animals to bacterial extracts as to sera nor so easy to produce anaphylaxis in sensitized animals by the use of bacterial extracts as with serum. This is accounted for by Zinsser on the basis of the fact that bacteria contain very little coagulable protein as compared with serum. The identity of bacterial anaphylaxis, however, with serum anaphylaxis, seems substantially proved by the additional fact that specific sensitiveness to bacteria can be passively transferred to normal animals by injections of immune sera and in the infected animals typical symptoms resembling serum anaphylaxis can be induced by injections with the appropriate antigen.

Whereas anaphylaxis can occur as a result of sensitiveness to bacterial proteins and does occasionally occur during the course of acute infectious diseases, such as rheumatic fever, scarlet fever, acute tonsillitis, etc., this is not the type of reaction which is ordinarily observed. The usual reaction is one of an inflammatory type, resembling more the much investigated tuberculin reaction. The difference between this (the ordinary reaction) in infectious diseases

and the urticarial reaction resembling serum sickness (the unusual reaction), can possibly be accounted for by the fact that contact between the individual and foreign (bacterial) products in an infectious disease is so much more gradual and constant than it is after an injection of serum that the patient, upon becoming sensitive to bacteria, gains tolerance for them through constant gradually increasing intimate contact and for this reason reacts toward them differently than he does toward one or several injections of serum.

When a human being or an animal is infected with the living microorganisms, he becomes sensitive to their products after a certain period of time and thereafter reacts toward them in a characteristic way whenever he comes into intimate contact either with the living bacteria or killed cultures of them or with filtered media in which the bacteria have grown and this whether such material is injected or applied to the conjunctival mucous membrane or to a scarified area on the skin. If the contact is gross enough, a local and constitutional reaction appears after twelve to twenty-four hours and resembles that which we ordinarily observe in local or general infections. Locally it consists of the classical signs of inflammation—rubor, dolor, chalor, tumor, and functio lesion.

This type of reaction was attributed by Koch in 1891, to additional injury to the already infected tissues by bacterial products; by Vaughan in 1908 to the liberation of nonspecific poisons by the parenteral digestion of proteins by specific enzymes developed under the influence of the foreign proteins of the infecting organisms; by Wassermann and Bruck in 1906 to harmful union of bacterial antigen and amboceptor attached to the infected tissues; and by Friedburger in 1910 to anaphylatoxins liberated from a combination of antigen and antibody through the action of complement. These ingenious theories need not be discussed in detail since they have been dealt with at length in other works and since we are here concerned primarily with the anaphylaxis-like reaction rather than reactions of the inflammatory type. A comparison of the two types of reaction, however, seems not amiss.

In animal anaphylaxis and in the human anaphylaxis-like reactions we have a condition characterized chiefly by erythema, edema, itching, contraction of nonstriated muscle, and shock which may prove rapidly fatal. The reaction is of rapid onset and subsidence,

and animals which survive are left in a state of antianaphylaxis and are thereafter for a time refractory to further contact with the offending agent. In the inflammatory type of reaction, however, we have cardinal symptoms, pain, swelling, redness, edema, and the constitutional symptoms of infection, all of which are of slow onset and slow subsidence and if the individual survives, we rarely find so high a grade of resistance that he is indifferent to further contact with the offending agent. As a further difference of importance may be mentioned the fact that anaphylaxis-like sensitiveness can be transferred passively to normal animals by serum injections, whereas in the inflammatory type of illness this is apparently not the case.

In attempting to explain these differences Zinsser points out that materials which elicit tuberculin-like reactions (such as boiled treated extracts) are chemically quite different from the coagulable protein bodies required for the production of anaphylactic sensitiveness and the anaphylaxis reaction. Furthermore, that in infections which produce tuberculin-like sensitiveness, the animal is more constantly under the influence of the foreign substances diffusing out from the growing focus and therefore, reacts quite differently from animals exposed to the influence of coagulable proteins absorbed from a site of an occasional injection. Zinsser suggests that because of the diffusibility of the substances causing tuberculin-like sensitiveness they should penetrate more deeply into living cells and for this reason give rise to a deeper seated harmful antigen antibody reaction than in the case of anaphylaxis. In the latter case, because of the large indiffusibile protein molecule the reaction should take place chiefly on the surface of the cells and result, for this reason, in a different type of reaction, both in time and in character.

## CHAPTER VII

## NATURAL HYPERSENSITIVENESS IN HUMAN BEINGS

### (General Discussion)

There exists in human beings a type of hypersensitiveness which appears spontaneously, which is remarkably similar to experimental anaphylaxis in animals. While the two conditions are very similar in many respects, the question as to whether or not they are identical in pathogenesis is still under discussion.

Human hypersensitiveness has apparently been observed and described in very early medical writings under a large variety of titles. In a splendid review of the literature on pollen disease, Koessler quotes Botallus who in 1565 reported a case in which the odor of roses caused headache, sneezing, and itching of the nose, Von Helmont who in 1577 described a case of seasonal asthma, Schneider who in 1662, and Benningerus who in 1673 wrote on the subject of rose catarrh. Koessler quotes many other early papers but states that Bostock in 1819 was the first to recognize hay fever as a clinical entity. Interesting to relate, Bostock thought the condition was caused by heat and sun rays (to be discussed in Part II). Blackley in 1856 commenced a remarkably accurate series of observations which lead him to state that hay fever was caused exclusively by pollen. He reproduced typical symptoms in himself, a sensitive individual, by the application of pollen and pollen solutions to the mucous membranes of the eyes, nose, and mouth. He also performed skin tests through applying dried pollen to a scarified area on the skin. This caused intense local itching and swelling which lasted about four days. Blackley furthermore studied the relationship between the number of pollen granules in the air and the severity of clinical symptoms by exposing glass plates covered with sticky material to the wind and determining the number of granules which were deposited within twenty-four hours. He drew the brilliant conclusion in his own case that symptoms varied with the increase or decrease in the pollen content of the air. Blackley's results were confirmed in 1903 by Dunbar who established beyond

doubt the rule played by pollen in the pathogenesis of hay fever and asthma. The paragraph which follows quoted from Koessler shows that Blackley left little for later observers to originate.

"Charles H. Blackley, a physician in Manchester, England, on the basis of exact analytical observation followed by very numerous and exceedingly cumbersome experiments, advocates the view that hay fever is exclusively caused by the pollen of graminaceae. Being subject to the disease, he tested on himself the pollen of about one hundred different species of grasses and flowers, in the fresh as well as in the dried condition, in different ways. He applied it to the mucous membranes of the nasal cavities, he inhaled it, he made a pollen extract and instilled it into the conjunctivae, applied it to the lips, tongue, and pharynx, and finally inoculated 'the upper and lower limbs with fresh moistened pollen.' Even when a minute quantity of pollen, such as 1/2000 gr., was applied to the mucous membrane of the nose, hay fever symptoms appeared in every instance. The pollen of rye caused more violent symptoms than that of grasses. The pollen of wheat and oats had about the same activity as that of grasses, while the pollen of barley had less power. The inhalation of the pollen of certain plants and grasses produced asthmatic attacks and constitutional symptoms. One drop of an extract of the pollen of gladiolus instilled into the conjunctiva and lids followed, but in thirty-two hours every trace of the trouble had disappeared. Applied to the pharynx, itching and congestion was produced within a half hour. Blackley performed further the first skin test with pollen. On rubbing the pollen into the scarified skin of the forearm and over the tibia, erythema with intense itching and swelling resulted, which lasted for four days. These effects, though common to all different kinds of pollen, varied considerably in intensity. The poisonous properties of plants stood in no relation to the effectiveness of their pollen in producing hay fever symptoms. Blackley observed further that a high temperature favored the growth of pollen, while a low temperature was unfavorable. From these experiments Blackley concluded that: (1) the pollen produces catarrhal and asthmatic symptoms in himself; (2) that the effect though varying in degree is common to the pollen of all plants experimented with, but the order of graminaceae possesses it in a markedly higher degree than the others. He raises the question if the granular matter of the pollen might not find its way through the mucous membranes of the respiratory tract and thus give rise to the constitutional disturbances that are noticeable in some cases.

"Having established these facts Blackley proceeded to investigate the relation between the quantity of pollen in the atmosphere and the intensity of symptoms. He exposed to the wind glass plates covered with a sticky mixture, and determined how many pollen grains were deposited in twenty-four hours. Experimenting between the months of April and August (1866), he found that between May 30 and August 1 the quantity of pollen increased gradually up to the last week in June, and then decreased. In his own case the symptoms of the disease rose and fell in exact correspondence to the increase or decrease of the amount of pollen in the atmosphere. He observed further that after a rainfall the quantity of pollen was considerably lessened. He observed that

about 95 per cent of all the pollen found on his glass slips belonged to the order of graminaceae. Inside his house, if the windows were closed, he found very little pollen. He established further that the very small amount of pollen in the atmosphere, observed prior to June 8, did not produce hay fever symptoms. He repeated all these experiments in 1867 and 1869, and in the country as well as in the city, and observed that in the city there was on the average 1/10 as much pollen as in the country.''

The first suggestion that human hypersensitiveness is related to anaphylaxis as observed in animals came from Weichhardt and from Wolff-Eisner in 1905 and 1906 in their discussions on the subject of hay fever. Meltzer in 1910, on the basis of the similarity between the bronchial constriction of asthma and that observed in animals dying in anaphylactic shock, suggested that true bronchial asthma was a phenomenon of anaphylaxis. Koessler at about the same time and independently of Meltzer, made the same observation, and in 1913, reported a case of asthma caused by hypersusceptibility to hen's egg.

It is hardly possible in a book of this scope to quote the many researches which have been responsible for the place this subject now occupies in practice of clinical medicine. The development has been largely one of elaboration and putting to practical use work initiated by the earlier writers.

In recent publications, Doerr, Coca, Cooke, and others have pointed out and emphasized differences between natural hypersensitiveness in human beings and artificially produced anaphylaxis in animals and have drawn the conclusion that the two conditions must be basically different in pathogenesis or at least, that the identity of the two conditions is as yet unproved. Others, such as Zinsser and Koessler, point out basic similarities which seem to them to overbalance the apparent differences. The differences which do exist might be accounted for, they believe, to a large extent by differences in the mechanism of reaction so commonly observed in different species of animals.

The salient features of the artificially produced sensitiveness in animals were enumerated in detail in the chapter on experimental anaphylaxis. The essential features of naturally acquired sensitiveness in human beings and the similarities and differences between them and animal anaphylaxis seem to be about as follows:

1. **Heredity.**—Heredity plays an important part in the development of sensitiveness in human beings. This has been mentioned

repeatedly even by some of the early writers, such as Wyman in 1872 and Beard in 1876. It was studied elaborately in 1916 by Cooke and Vander Veer who found that the constitutional peculiarity which makes probable the development of hypersensitiveness is transmitted according to Mendelian laws as a dominant characteristic. Other important contributions made in their study were the facts that the form of hypersensitiveness in the parent is more often different from that in the offspring than it is identical to it and that with bilateral inheritance symptoms appear in the offspring at a much earlier age than when inheritance is unilateral—in other words, "the more complete the inheritance, the earlier the manifestations."

In contrast to the above, inheritance in guinea pigs either plays no part at all or must involve 100 per cent of animals, for all guinea pigs are alike in their capacity for being sensitized. In other animals, such as rabbits, the ratio is much smaller and for monkeys is very small indeed—in fact, some question the possibility that monkeys can be sensitized at all. Human beings, if they are to be compared with animals, in this respect must be of two types immunologically. First, those having a mechanism (analogous to that of guinea pigs) which, under suitable conditions, is capable of becoming sensitive; and second, those (analogous to monkeys) who are apparently incapable of becoming sensitized or at least, only with great difficulty.

2. **Natural and Artificially Acquired Sensitiveness.**—Anaphylactic sensitiveness in certain animals occurs consistently as a result of treatment with foreign antigens. In human beings it rarely occurs as a result of treatment, but does occur spontaneously in a large percentage of individuals and often before the patient has had apparent contact with the offending substance. It would be difficult to determine whether or not animals become spontaneously sensitive. The fact that sensitiveness could occur spontaneously, however, would be suggested by the work of Rosenow and Anderson who sensitized animals to horse serum by the feeding of horse serum.

Whereas it is common for human beings to become sensitive spontaneously, it is quite apparent that it is extremely difficult to sensitize them artificially. The truthfulness of this statement should seem evident when we consider the enormous number of substances

of all varieties which are repeatedly injected intracutaneously, subcutaneously, and intravenously into human beings by physicians without the appearance of symptoms in any way suggestive of anaphylaxis. However, human beings are occasionally sensitized artificially. It is not rare, for example, to find that sensitiveness develops in individuals of allergic strain after the repeated intravaneous use of drugs, such as salvarsan. This sensitiveness is apparently permanent and because of it, the use of salvarsan occasionally has to be discontinued.

As previously mentioned, some individuals are found sensitive to substances with which they have apparently never come in direct contact. The correctness of this statement can well be questioned, however, when we consider that breast-fed infants are frequently found sensitive to and are made ill by foods which they have never eaten but which make up part of the mother's diet. It is not impossible that sensitiveness is often acquired *in utero* due to contact with substances absorbed from the mother's alimentary tract and elsewhere. For this reason, it is almost impossible to eliminate the possibility of previous contact in sensitive individuals.

3. **Permanence of Sensitiveness.** Anaphylactic sensitiveness in animals may last during the life of the animal. It becomes less marked, however, with time, and should the animal live for a great number of years, as do human beings, it would probably be found that sensitiveness artificially produced is not permanent. Sensitiveness in human beings, however, is apparently permanent—at least, it lasts in the average case for a great number of years. While this is true of the contact type of reaction, such as pollen disease and other surface reactions caused by direct contact with air-borne substances, it is not so true of the general reactions, such as those which occur as a result of the ingestion of certain foods. Disappearance of the latter type of sensitiveness may be accounted for possibly by some change in the digestive ferments or mode of absorption of the offending material or possibly by the development of tolerance in the patient induced by frequent gross contact. This, of course, would not apply to air-borne substances which are not affected by digestive juices and which are rarely absorbed in sufficient quantity to give rise to tolerance.

4. **A Comparison of Agents Capable of Sensitizing Animals and Human Beings.**—It is generally recognized that sensitiveness in ani-

mals artificially induced depends upon treatment with antigenic substances. Human beings, on the other hand, can become naturally sensitive to a great variety of substances both antigenic and nonantigenic—even to the action of inorganic salts and even, as will be shown in Part II to the action of physical agents, such as light, heat, and cold.

This striking difference between human beings and animals may be more apparent than real. It has been shown in work previously referred to, especially that by Landsteiner, that animals which have been sensitized to proteins altered artificially by the introduction of nitro or bromide groups, will react to the altered proteins upon second injections but not to the original. It seems possible, after all, that human beings may be affected directly only by antigenic substances and that sensitiveness to nonantigenic substances and to the action of physical agents might come about through the medium of altered proteins. The fact that animals do not react similarly to nonantigenic agents may be explained, possibly, by the fact that animals are desensitized so much more easily and quickly than human beings. Should an animal, for example, be sensitive to a protein altered by bromine or by light he could hardly be expected to react upon contact with bromine itself or light, for under the influence of bromine or light with the gradual formation of the altered protein a condition of antianaphylaxis would be induced before the dose elaborated (of altered protein) was large enough to cause reaction. I have encountered this difficulty, I believe, in endeavoring to sensitize animals to the action of physical agents, such as light. I think it is possible that animals can be sensitized to light by treatment with light. However, I have been unable to give quickly a dose of light large enough in any case to cause an immediate reaction—in fact, I believe rather that I succeeded in inducing tolerance for light (normal guinea pigs can be killed by exposure to noonday summer sunlight for from twenty to thirty minutes). The fact that human beings can react to such agents as they are encountered under natural conditions may be accounted for possibly by the fact that natural sensitiveness in people is so much greater in degree than that artificially produced in animals and furthermore, tolerance in human beings is much more difficult to induce.

5. **Degree of Sensitiveness.**—Whereas sensitization of an animal may take place under the influence of almost unbelievably small doses of foreign protein, even .000001 c.c. of serum, a shock dose must be considerably larger in every case. Furthermore, the dose must be given with sufficient rapidity to cause symptoms before a state of antianaphylaxis can be developed. A hypersensitive animal can be desensitized, according to Besredka, by giving antigen per rectum or by giving infinitesimal doses at frequent intervals or by giving relatively small doses subcutaneously, or by giving a dose intravenously with great slowness. A dose which may prove fatal if given intravenously may be harmless if given subcutaneously because the slowness of absorption allows the development of antianaphylaxis. This is not the case in human beings. Many individuals sensitive to substances such as egg, fish glue, or pollen may react violently to unbelievably small quantities of the offending substance. Horse sensitive cases, for example, react to the minute quantity of epithelium in the air around horses, pollen sensitive cases to the minute amount of pollen in the air. In a case reported by Boughton, a fatal issue followed the intravenous injection of 1 minum of horse serum and in one reported by Cooke, the intracutaneous injection of .01 c.c. of a solution of fish glue caused death. In a case to be referred to by the writer, an alarming reaction followed the application of a little fish glue to the skin and this in spite of the fact that it was washed off almost immediately. Sensitiveness of this degree is unknown in animals.

6. **Specificity of Sensitiveness.**—While specificity is a marked characteristic of artificially induced sensitiveness in animals, it is not comparable with that observed in human beings. Animals sensitized to a protein, for example, will react to the homologous protein of closely related species (Kraus, Doerr, and Soma; Wells and Osborne). Animals sensitized to the tall ragweed may react to injections of extract of short ragweed and vice versa (Harrison). Specificity in human beings is far more highly developed than this —at least to substances as they are encountered naturally. I studied one case very sensitive to home grown strawberries who could eat freely of strawberries grown in the south, another sensitive to cantaloupe grown in a limited district who could tolerate cantaloupe of other districts. A most marked example of specificity was that of a patient sensitive to Iva xanthiifolia of a neighboring

state who was relatively insensitive to the identical weed growing in this district. His symptoms not only disappeared upon coming to this district but skin tests made even with a 5 per cent extract of pollen collected here caused no reaction. The skin reaction following the use of a minute amount of the same pollen collected in his own state gave an intense reaction. It is the usual experience for ragweed cases of this district to be symptom free in states of greater altitude, even if their contact with ragweed of such districts is intimate. Specificity in animals is apparently not so marked as this. It might be more marked, however, if absolutely pure substances could be used both in sensitizing and for the shock dose (materials such as egg white used for sensitizing animals, are usually mixtures of a great many different bodies rather than one pure chemical substance).

Specificity is not so marked a feature of sensitiveness to foods as it is of sensitiveness of air-borne substances. This is probably due to the fact that patients sensitive to air-borne substances are usually sensitive to the substance as it exists naturally while patients sensitive to foods are frequently sensitive to bodies common to several foods which are related biologically or to digestive products common to several foods or to several proteins. Even normal individuals are sensitive to histamine and similar bodies which are elaborated normally in the intestine through the action of the digestive ferments and putrefactive bacteria upon protein foods.

7. **Multiple Sensitiveness.**—Animals may be sensitized to one or to several proteins simultaneously. Human beings, likewise, may become spontaneously sensitive to more than one frequently to each member of a group of somewhat similar substances and frequently to several groups of substances. For example, individuals sensitive to foods may also be sensitive to air-carried substances, such as pollen. In fact, in one hundred pollen cases, 45 per cent showed skin sensitiveness to other agents (in the following ratio: meat 7 per cent, eggs and dairy foods 10 per cent, vegetables 45 per cent, fruits 20 per cent, fish 2 per cent, condiments 5 per cent, nuts 7 per cent, grains 30 per cent, animal dander 30 per cent, bacteria 18 per cent, dust 10 per cent, extract of weeds 5 per cent). Though tests showed skin sensitiveness in the ratio above mentioned, very few of the patients were actually sensitive to the many substances as encountered naturally. As a rule, they were clini-

cally sensitive to one or several substances as encountered naturally but rarely to the large number to which they reacted cutaneously.

8. **Passive Transfer of Sensitiveness.**—Animals can be sensitized passively to a given protein by an injection of serum of an animal which has been previously sensitized to the protein. For example, untreated normal guinea pigs can be sensitized to horse serum by an injection of serum of a guinea pig which has previously been sensitized to horse serum. Whether or not this is true in the case of human hypersensitiveness is a question. Considerable difficulty attends its proof. It is not a justifiable experiment to transfer human blood by transfusion to normal or allergic individuals, because of the fact that patients subject to allergy are not good subjects for blood transfusion, especially if hypersensitive donors are to be used. The experiment could easily result disastrously with symptoms of shock within a few moments. However, there are isolated instances in which emergency or accident has caused hypersensitive individuals to be transfused. In a case reported by Ramirez, a normal individual was transfused with 600 c.c. of blood from a donor who was horse sensitive. Two weeks afterward the patient went for a carriage ride in Central Park. Almost immediately upon entering the carriage, she experienced difficulty in breathing which developed within five minutes into a marked case of bronchial asthma. A physician was called and epinephrin administered—after which the paroxysm came to a rapid end. It recurred later in the evening.

The patient was then tested with a large number of food and bacterial extracts and pollen. All gave negative results. Tests with a very dilute extract of horse dander, however, gave a hive measuring one and one-half cm. in diameter. The donor, when tested with an extremely dilute solution of horse serum, gave a reaction 6 cm. in diameter.

Ramirez stated in a letter recently that sensitiveness in this patient disappeared after a few days and that soon afterward she died of pernicious anemia. Because of this, he was unable to carry out the extensive study which the case merited. He stated also that he has since then transfused several patients from donors who were subject to allergy in one form or another without evidence of passive transfer.

Preusnitz and Küster found that the skin of a normal individual can be passively sensitized locally by an intracutaneous injection

of the serum of a hypersensitive human being and that passive sensitiveness so transferred is specific for the substance to which the donor is sensitive. Coca* and his associates, in studying this phenomena, found that the skin of all normal individuals is not receptive—in other words, in a certain small percentage of individuals the skin cannot be sensitized passively. They were able to confirm the work of Preusnitz and Küster, however, in a majority of individuals and, furthermore, found that the skin could be separately sensitized in one locality to several substances at the same time and that such areas would react separately to each substance. Furthermore, that the sensitized skin could be desensitized separately for each substance by injection with suitable solutions and that desensitization was specific for the substance used.

## Summary

From the data which precede, it can be seen that anaphylaxis in animals and hypersensitiveness in human beings present many remarkable features in common. It would seem indeed remarkable if the two conditions are not closely related. It cannot be contended, however, at the present time that the two conditions have been conclusively proved to be identical.

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*Personal communication.

# CHAPTER VIII

## THE RELATIONSHIP BETWEEN HYPERSENSITIVENESS AND OTHER DISEASES

It would be interesting to know what conditions other than heredity play a part in the development of hypersensitiveness. Furthermore, it would be interesting to know whether or not hypersensitiveness has an influence upon an individual's susceptibility to other diseases. For the purpose of determining this, if possible, the records of a series of cases having unquestionable chronic manifestations of reaction, such as hay fever, asthma, or hives, were reviewed and notes made concerning conditions other than allergy which were found.

It was observed at the outset that patients subject to hay fever, asthma, or hives had more of certain diseases and less of others than an equal number of patients of the same age who were examined according to the same routine for miscellaneous complaints. Goiter, hypertension, hypotension, achylia gastrica, bronchopneumonia, nasal polyps, acute and chronic nasal sinus infection seemed more common while chronic infections, such as syphilis and tuberculosis, seemed unusually rare.

The records of the chronic allergy cases were then divided into four groups, the seasonal pollen group, the perennial nasal and bronchial group, and the two physical groups (to be described subsequently, both the contact cases and reflex like cases). The diseases found were tabulated and the results compared with those obtained from a similar compilation of 1000 chronic medical cases reported at an earlier date and with those obtained from a routine examination of 100 bank employees because of miscellaneous complaints.

It is recognized that statistics taken from records are not accurate unless the records are made for a specific purpose. Also, that histories, especially family histories, are never more than relatively correct and finally, that a comparison made between groups of cases of different ages and for different reasons is necessarily less

accurate than a comparison made between patients of the same age and examined for one specific purpose. However, the differences noted between these groups of cases were too gross to be accounted for by such sources of error.

### Pollen Cases

The pollen cases averaged thirty-three years when examined, while the perennial cases averaged thirty-eight. Many of the pollen cases were children. The medical cases were a little older when examined than either group of allergy cases.

It was interesting to note that of 100 pollen cases reviewed, 56 per cent gave a positive family history of hay fever, asthma, or hives, 40 per cent gave a history of seasonal asthma in addition to hay fever; 14 per cent a history of urticaria or angioneurotic edema, and 6 per cent a history of chronic eczema.

In 20 per cent the blood pressure was below 110. This hardly represents a correct estimate, however, of the effect of pollen disease upon blood pressure, since in the majority of cases the estimations were made out of the pollen season. Hypertension was found in one case only.

Oral sepsis was found in only 14 per cent of cases and this was slight in degree. Furthermore, tonsils which seemed to be diseased were observed in only 14 per cent. This is considerably below the average observed among the bank employees examined in which oral sepsis of much greater degree was found in 31 per cent of cases and bad tonsils in 17 per cent. Both of these are considerably below the average found in patients observed in consulting medical practice previously reported (in 1918) in which oral sepsis in high grade was found in 66 per cent of cases. It seemed quite possible that the younger average age of pollen cases would account for some difference in these statistics, but hardly for differences so gross in degree.

A deviated nasal septum was found in 32 per cent of cases. This was not gross enough to be of serious import to normal individuals, but in patients subject to edema of the membranes of the nose, it might have interfered with proper aeration of the sinuses. However, chronic nasal sinus infection could be demonstrated in only 6 per cent of cases and nasal polyps were found in only 10 per cent. It will be observed later that the perennial cases differ markedly

from the seasonal cases in this respect and show a much higher ratio of polyps and chronic nasal sinusitis.

It is interesting to mention that active syphilis was not found in a single one of the 100 cases of seasonal hay fever tabulated and only one case of active tuberculosis. The one case of active tuberculosis had shown a remarkably favorable course over a period of twenty years.

### Perennial Cases

The statistics obtained from a review of 100 perennial cases, the great majority of which gave negative sensitization tests, were quite different from those of the seasonal cases. This difference might be accounted for to a small extent by the greater average age at which the perennial cases were examined.

Forty-eight per cent of the cases gave a family history of hay fever, asthma or hives. Fifty-four per cent had nasal reaction when examined. Eighty-one per cent had bronchial asthma. Twenty-four per cent gave a history of urticaria, and nine per cent gave a history of eczema.

Twelve per cent had goiter. Of these, six per cent had definite toxic symptoms.

The blood pressure was normal in 40 per cent of cases, was below 110 in 43 per cent, and above 150 in 17 per cent of cases. In two of these, it exceeded 200.

Thirty-three per cent were overweight. This is a very high ratio as compared with individuals having miscellaneous complaints.

Twenty-seven per cent had oral sepsis, but as a rule only slight in grade. Nine per cent had bad tonsils. Both these ratios were evidently very markedly reduced because of the fact that in a great many cases both teeth and tonsils had been removed prior to the time at which examinations were made in an effort to cure their illness.

Thirty-three per cent showed deviated nasal septum, 24 per cent had nasal polyps, 27 per cent had definite unmistakable evidence of chronic nasal sinus infection. Twenty-one per cent gave a history of marked predisposition to coryza, 12 per cent dated the onset of their illness definitely to an attack of "acute pneumonia." Many gave a history of "pneumonia" although our notes regarding this are incomplete. A considerable number gave history of repeated

attacks of "pneumonia" and a considerable number had "pneumonia" while under our care or subsequently.

A gastric analysis was made in 24 cases because of stomach symptoms. Of these, 12 showed a complete achylia, six a free acidity per cent below 5 and six normal acids.

Among the 100 cases, there was observed only two cases of specific disease and only one of active tuberculosis. In each case the symptoms were mild in grade.

### Physical Cases

Of thirty-seven cases examined, who were hypersensitive to the action of physical agents, ten were contact cases and twenty-seven reflex-like cases. A positive family history of reaction of some type was obtained in 90 per cent of the contact cases and in 66 per cent of the reflex-like cases. The contact cases were relatively normal physically except for two cases of hypertension.

The ten contact cases were all subject to urticaria, one to eczema, one to asthma, and one to nasal reaction.

Of twenty-seven reflex-like cases, 63 per cent had nasal reaction, 47 per cent had bronchial asthma, 37 per cent were subject to urticaria or angioneurotic edema, and only two cases had dermatitis.

The blood pressure was normal in the contact cases except for two who had mild hypertension. Four of the reflex-like cases had a blood pressure exceeding 150 and two below 100. The remainder were normal.

Ten of the cases had a deviated nasal septum but not one single case had evidence of chronic nasal sinus infection. In only four cases were the tonsils bad. Oral sepsis of marked degree was found in six cases.

Syphilis and tuberculosis were not observed in a single case.

### Summary

The statistics just reported are interesting in showing a definite increase in the number of certain conditions among hypersensitive patients and a paucity of others.

The following conditions were unusually common:

1. Achylia gastrica in perennial cases.

2. Hypertension and hypotension in the perennial cases.

3. Obesity in the perennial cases.

4. Nasal polyps and chronic sinus infection in the perennial cases.

5. Acute infections of the respiratory tracts, such as coryza and bronchopneumonia in the perennial cases.

While the above-mentioned conditions were unusually common, chronic infections, such as tuberculosis, syphilis, advanced oral sepsis, and chronically infected tonsils were unusually rare.

In order to verify the accuracy of this latter rather surprising result, the records of 500 cases of chronic hay fever, asthma, and urticaria which had been examined carefully for both tuberculosis and syphilis were reviewed. Among these cases seven had proved active tuberculosis and in three tuberculosis was suspected but not proved. Of the seven cases of active tuberculosis, all were of long standing, all afebrile, and all were able to attend to their business affairs. Only one of the tuberculous patients observed during a period of ten years died and this one of a cardiac death which occurred as a result of an embarrassed pulmonary circulation due to a densely fibrosed lung. The patient at the end was afebrile, had cardiac dyspnea, positive congestion of the organs, anasarca, and cyanosis.

Nine of the five hundred allergy cases had active syphilis of long standing. All responded well to therapy and not one single case showed any evidence whatever of tabes or paresis. In fact in my entire experience with allergy I have observed one case of tabes dorsalis in a patient subject to frequent reaction.

These facts are grossly different from cases observed in consulting medical practice examined in the same way. Of 1000 cases examined prior to 1918 and tabulated, active syphilis was found in 13 per cent of cases. Of these, half or over 6 per cent of the total 1000 cases, showed definite evidence of tabes or paresis.

Eight per cent showed evidence of active tuberculosis and the majority of these has terminated fatally. While this stands in marked contrast to the incidence of both syphilis and tuberculosis among allergy cases ( in each case, less than 2 per cent), it stands in much greater contrast to the remarkably favorable course of the illnesses observed in each of the allergy patients who were so afflicted.

## Conclusions

It seems to me that the data at hand justified several conclusions.

*First.*—That allergy may be a primary or contributory factor in the etiology of a certain class of cases of hypertension and hypotension.

*Second.*—That it is probably an etiologic factor in the pathogenesis of nasal polyps and chronic nasal sinus infection. This is believed to be a mechanical affair. Edema of the membranes of the nose, especially during the winter months and especially if associated with deviated nasal septum, could easily predispose mechanically both to the formation of polyps and then to acute and chronic sinus infection. This seems true of perennial rather than of seasonal cases.

*Third.*—That patients with perennial hay fever and asthma are predisposed to acute infections in the respiratory tract, such as coryza and bronchopneumonia. It is possible that this is also a result of mechanical obstruction in the sinuses and bronchial tree resulting from the swollen membranes. It is believed, however, in addition to this that chronic reactive cases are immunologically different from the normal and are actually predisposed to acute infectious diseases.

*Fourth.*—That patients with chronic allergy have a relative immunity to chronic infections, such as syphilis and tuberculosis and that in them these diseases run a remarkably favorable course.

*Fifth.*—That allergy may play a rôle in the etiology of a certain class of cases of obesity and of achylia gastrica.

## CHAPTER IX

## THE NATURE OF AGENTS WHICH SENSITIZE HUMAN BEINGS AND THE FACTOR MODE OF CONTACT

Animals can be sensitized apparently solely by antigenic substances. This is apparently not true of human beings, who can be sensitized by nonantigenic substances—in fact, even by inorganic matter—in fact, even by the action of a physical agent (see Part II).

In spite of the above statements, a question arises as to whether or not human beings, like animals, can be sensitized by substances other than antigenic. It seems logical to believe that human beings and animals should be alike in this respect and that the effect of inorganic matter and physical agents might be indirect, rather than direct—that is, that they are effective through the elaboration of a new antigenic substance which directly causes sensitiveness and reaction.

Relatively little is positively known concerning the physical or chemical make-up which characterizes agents which can sensitize human beings. More is known concerning their location.

It is not difficult in many cases to trace the source of an illness to contact with substances, such as milk, egg, pollen, animal hair, feathers, cottonseed, orris, or flax or to constituents of these which can be extracted with salt solution or glycerine, or even to relatively well purified constituents, such as ovomucoid, egg white, or lactalbumin. It is very difficult, however, to identify and place the blame on the chemical body actually responsible. It is difficult even to classify it as protein or nonprotein, organic or inorganic. The mere fact that an individual reacts to a certain protein cannot be looked upon as conclusive evidence that the suspected protein is actually the cause of reaction for it is perfectly possible that the offending agent simply accompanies certain proteins, just as diphtheria antitoxin accompanies certain globulins of the serum. The truth of these general statements can be illustrated by the following examples.

Infants made ill by milk are frequently not sensitive to any of the gross constituents of milk or even to any of the usual con-

stituents of milk, but to some article eaten by the mother or animal furnishing the milk (O'Keefe, Shannon). Patients sensitive to honey are frequently not sensitive to honey of all varieties, but only to honey of one source, such as clover or buckwheat. Egg sensitive cases in instances recounted to me by Gerald B. Webb and by Ray Matson were made ill by the meat of a hen but tolerated well the meat of a rooster. A case of the sort which I studied was sensitive to every part of the egg, raw or cooked, could tolerate rooster meat but invariably reacted to hen meat with a severe attack of asthma. One patient made ill by aspirin was found sensitive not to aspirin itself, but to an impurity contained in only one of five preparations used in testing. No better illustration can be given of the elusiveness of substances which sensitize than that of salvarsan reactions caused, not by salvarsan, but usually by the infinitesimal amount of impurity contained in distilled water. These examples should illustrate the extreme difficulty of actually discovering the primary offender in sensitive cases and should convince one that he should feel content in the present day if he knows its location and source.

With this in mind, one hesitates to say too much concerning the nature of substances which can sensitize. Certain it is that the majority can be violently poisonous in almost infinitesimal doses. Patients sensitive to horse dander may be made ill by the almost infinitesimal quantity in the air around horses and patients sensitive to pollen by the minute amount of pollen in the air. Occasionally the injection of a .1 c.c. of a 1 to 10,000 solution of pollen causes a severe reaction in a sensitive patient. As previously mentioned, the intravenous injection of one drop of horse serum in a horse sensitive patient and the intracutaneous injection of 0.01 c.c. of a solution of glue in a glue sensitive case has been known to cause death. One of my most violent reactions followed the application of fish glue to the skin, and this in spite of the fact that the glue was washed off after a few moments.

Since agents directly or indirectly responsible for reaction have been traced to such varying factors as light, cold, heat, and friction (to be described subsequently), to almost innumerable varieties of vegetable and animal matter (apparently both protein and nonprotein), and even to inorganic salts, smoke, gases, dust, etc.,

we are forced to believe that the nature of substances which can sensitize and cause reaction is probably varied.

Some substances have a greater faculty for sensitizing and causing reactions than others. Pollen, for example, sensitizes more frequently than other parts of a plant. Lactalbumin, or some substance which accompanies it, sensitizes more frequently than other fractions of milk, and ovomucoid more frequently than other parts of egg. These facts do not necessarily indicate that the faculty for sensitizing and causing reactions resides in the chemical make-up of the body. It may be due to mode of contact. For example, agents responsible for the more severe reactions are usually bodies which are not commonly met with, or if met with commonly, are encountered in traces only. It is rare to find individuals sensitive to the bulky constituents of the commonly eaten meats, vegetables, or fruits. It is much more common to find sensitiveness to the less common articles of diet, such as radishes, lettuce, celery, onions, shad roe, caviar, paprika, buckwheat, etc. Furthermore, patients made ill by commonly eaten foods, such as milk, eggs or beef are usually sensitive to one of the smaller constituents thereof. Patients sensitive to wheat are more commonly sensitive to some constituent of the husk than to white flour, and in the case of fruits or vegetables, more frequently to some constituent of the peeling than to substances in the edible portion. This all might be explained possibly by assuming that should patients become sensitive to the bulkier constituents of the commonly eaten foods, they would gain tolerance for them through frequent gross contact.

Agents which cause reaction sometimes become inert when heated and less offensive when the patient takes acids or alkalies. Occasionally the reverse is true, that is, that the offending agent is more active when the patient takes acids or alkalies. This observation should harmonize with theory when we consider the large number of chemical bodies which are liberated, volatilized, or precipitated by such agents.

One gains an impression that split products formed either by digestion in the alimentary canal or by parenteral digestion after absorption are frequently responsible for reaction. This is possibly true also of products of anabolism or chemical combinations formed either in the alimentary tract or in the body proper. One might surmise, however, even here, that in case an individual becomes

sensitive to a common split product formed and absorbed in bulk he would gain tolerance for it through gross contact, and that split products which might be presumed to cause reaction most frequently would be those ordinarily produced in traces or those which do not frequently gain entry in bulk to the body proper through absorption.

Vaughan, in treating a variety of proteins of different sources with sodium alcoholate, obtained a body from each which was toxic for normal animals. The poisons thus formed seemed to have the same physiologic action regardless of source. Eustis found that histamine, a nitrogenous body formed through the action of putrefactive bacteria upon protein, will produce hives and asthma in normal people, and suggested that absorption of this under certain abnormal conditions, is the common cause of each disorder. Koessler found that a lethal dose of histamine is contained in the normal intestinal tract and assumes that, although there, it is harmless because it cannot reach the general circulation under normal conditions.

Apparently the reverse of this are the results of Walker and Wetmore who found that reaction-producing substances are frequently destroyed by digestion. I observed a patient who was sensitive to a number of foods and who constantly gave positive delayed reactions when tested either clinically or intracutaneously. Gastric or pancreatic digestion of extracts of the foods to which she reacted not only failed to hasten the time of appearance of reaction upon injection but actually made the extracts inert. These apparently contrary results are not out of harmony with existing theories. They seem rather to indicate the polymorphic character of agents which can sensitize and cause reaction and that more than one mechanism may be involved in the pathogenesis of reaction itself.

One again encounters difficulty when he endeavors to determine whether an agent proved responsible for an illness is a direct or indirect cause of reaction. For example, in one patient in whom hives invariably followed exercise, one might have assumed that exercise was the primary factor. However, it was proved that exercise produced the reaction through heat production. At least, the reaction was always associated with a rise in temperature and could be prevented by the application of cold water or ice to the

skin. In another patient sensitive to some of the volatile oils, a typical attack of coryza could be brought on by the use of an enema containing salt. She was not made ill, however, by the use of enemas made isotonic with soda instead of salt. Furthermore, she was not made ill by the use of ordinary amounts of salt by mouth. It is possible in this case that saline enemas provoked the absorption of some chemical body from the intestinal tract to which she was hypersensitive but which under natural conditions was not absorbed. To say the least, salt was probably not the direct cause of the reaction.

Some individuals develop a tendency to react to a great variety of substances. In view of the fact that the great majority of sensitive cases react clinically to only a few agents, one must believe that such cases of gross multiple sensitization are probably, in reality, sensitive to one or to a few agents which are widely distributed in nature. One patient who reacted to almost every variety of food was found eventually to be sensitive solely to foods rich in purins.

Many patients react to substances which have in common only a liability to cause shock, such substances, for example, as human blood or therapeutic sera when given intravenously. Serum contains an enormous number of substances in traces, and it is not surprising that many individuals should react to it.

Children rarely react to foreign sera, salvarsan, or blood transfusion. As age advances, this freedom from the likelihood to react is lost and when mature age is reached, reactions become rather common. This is probably due to the fact that allergy cases, with age, develop hypersensitiveness to an increasing variety of substances and react when contact with the substances to which they are hypersensitive is brought about, either directly or indirectly by intravenous therapy. Whatever the cause, certain it is that allergy cases cannot be treated indiscriminately with intravenous medication as can infants and individuals who give negative past and family histories of the condition. In more than 50 per cent of cases observed by me which reacted severely immediately after the use of salvarsan or blood transfusion, a past or family history of hay fever, asthma, or hives was obtained. The practical importance of this fact justifies a statement that in patients having a past or family history of hay fever, asthma, or hives a preliminary dose of

adrenalin is indicated whenever transfusion or the intravenous use of serum seems urgent enough to justify its use.

## Requisites for the Recognition of an Agent Responsible for Reaction

When one has in mind the various commonplace facts which can lead him into error when endeavoring to discover the real agent responsible for reaction, he is naturally inclined to become conservative and frequently doubt whether or not he has the actual fundamental cause in hand and, if so, whether its action is direct or indirect. Even when history, clinical examinations, skin testing, clinical testing, and therapeutic testing all point in the same direction, he may yet be in error. However, if the following requisites are complied with before conclusions are drawn, it seems that error should at least be reduced to a minimum.

*First.*—That removal of contact with a suspected substance be associated with relief of symptoms.

*Second.*—That symptoms recur during a well period if the patient is again brought into contact with the suspected substance in a more or less natural way.

*Third.*—That local exhaustion of a tissue follows reaction due to local contact with the suspected substance.

*Fourth.*—That tolerance for the substance with relief of symptoms be produced by specific treatment with it.

In illustration may be mentioned the fact that if ragweed pollen is suspected as the cause of hay fever it should be possible:

*First.*—To relieve the patient of symptoms by removing him from the ragweed district.

*Second.*—Symptoms should recur if he is exposed naturally to ragweed pollen of the air.

*Third.*—The application of ragweed pollen extract to the nose should give rise to reaction, and this should be followed by exhaustion of the tissues locally so that further application of the extract should give rise to less or no reaction.

*Fourth.*—Appropriate treatment of patient with ragweed pollen extract subcutaneously should give rise to tolerance so that the patient should not react further to the ragweed pollen of the air.

## CHAPTER X

# POLLEN ABUNDANCE AND POLLEN DISEASE (A BOTANIC SURVEY OF KANSAS CITY, MISSOURI)

A limited number of individuals become sensitive to pollen. The proportion has been estimated by Scheppegrell as about 1 per cent. Once sensitive they are liable to react with ocular, nasal, bronchial, pharyngeal, or cutaneous symptoms whenever they come in contact with the pollen to which they are sensitive.

Sensitiveness to pollen is remarkably specific—in fact, so much so that a patient sensitive to a certain weed in one district may not react to the same weed growing in another district. This is not out of line with our knowledge of specificity as previously alluded to and is not stranger than the fact that individuals sensitive to cantaloupe of one district can often eat with impunity cantaloupes growing in other districts or that patients sensitive to strawberries of one district can often eat with impunity strawberries grown in other districts.

For the careful study and treatment of pollen diseases, the aid of a competent botanist is almost essential. Flora varies so greatly in different geographic districts, in the different states of a given district, different counties of a given state, and even in different areas in a county that the knowledge gained from a survey made in one area cannot be applied to other areas unless the many essential factors which influence the growth and pollination of plants are almost identical. There is even a wide variation in the flora in different parts of a city. This variation, however, is chiefly important to patients who frequent neighborhoods near weed patches and is of little importance to individuals who live several blocks or more from profuse vegetation. It has been shown by Scheppegrell in his pollen plate studies made in an aeroplane, that pollen is carried to great heights and for considerable distances by air currents. He found that pollen of the air at an altitude of over five thousand feet is almost as abundant as it was near the ground and that pollen can easily be carried for a distance of fifteen miles by wind. For this reason, climatic conditions and direction of air

currents are more important factors as a rule to patients in a certain neighborhood than is the distribution of weeds in that neighborhood unless it so happens that they reside near or in the midst of weed patches.

A thorough knowledge of the pollinating plants of a district is almost essential to the successful treatment of pollen disease in that district. Surprising as it may seem, there have been few complete botanic surveys reported thus far in the United States from which physicians can gain this knowledge. It is not possible in a book

Fig. 1.—Illustration of the type of weed which furnishes large quantities of wind-borne pollen. The haziness to the left is a cloud of pollen granules dislodged by a slight blow. It illustrates how great is the quantity of pollen liberated on windy days around weed patches. It was estimated that a patch of weeds 20 ft. square can liberate one pint of pollen within a period of three days.

of this scope to summarize even the surveys which have been made. This would be as futile as an effort to summarize the geologic surveys of the different states. For this reason, the reader is advised to depend upon surveys made locally in his own district by capable botanists rather than upon any general information which can be gained from this book.

However, since certain rules apply in general to pollen production and pollen disease in most botanical areas and since many cities

have in general many essential climatic and geographic features similar to ours, the following survey of Kansas City's district which was made with the help of Mr. O. C. Durham and Mr. B. F. Bush will be given in some detail.

In the making of a botanic survey, it appears evident at the outset that the flora of a given district varies from year to year according to weather conditions, not only in abundance of growth, but also in dates of pollination. The flora in different districts, of course, varies not only with the geographic situation itself, but also with altitude, climate, the seasons, rainfall, topography of the land,

Fig. 2.—Illustration of a type of plant which, although conspicuous, furnishes very little pollen. Flowering plants are rarely factors in the causation of pollen disease and cause illness only when sensitive patients come into intimate contact with the plant. Pollen of flowering plants, such as goldenrod, dandelion, daisies and sunflower, is carried by insects as shown in the illustration. The granules are usually too sticky or too heavy to be carried far by wind. Some are furnished with heavy spicules which cause them to adhere tightly either to the plant or to objects which touch the flower.

soil conditions, and conditions that result from cultivation and habitation. For this reason, the following facts concerning this district are mentioned: Kansas City is an inland city of about 500,000 inhabitants, of 39 degrees north latitude, of between 800 and 1000 feet altitude, has a temperate climate with four seasons, and an average rainfall of 37 inches a year. The summer temperature frequently reaches 90° F. to 100° F., and winter temperature occasionally falls to 0° F. The topography of the land is hilly, with

Fig. 3.—Short ragweed (Ambrosia elatior). The most common pollinating weed of this district. It grows best in sunny dry places.

Fig. 4.—Leaf and blossom of short ragweed.

Fig. 5.—Giant ragweed (Ambrosia trifida). Less common than short ragweed, but a more abundant pollinator. It grows best in slightly moist and shady places.

Fig. 6.—Giant ragweed, leaf, and blossom.

Fig. 7.—Southern ragweed or roadweed (Ambrosia bidentata). A distinct species of limited geographical distribution; a good pollinator.

Fig. 8.—Southern ragweed leaf and blossom.

a small proportion of level river bottom land, a rather small proportion of marshy land and very little natural prairie, sandy, or rocky land. The soil is largely under cultivation and is, to a large extent, suitable for cultivation. In the city are many vacant lots covered with weeds.

Experience teaches one that the plants chiefly responsible for pollen allergy are those which produce in greatest abundance a light, dry pollen which can be held in the air for a long period of time. Heavy pollen and oily pollen are not carried far in this way

Fig. 9.—Western ragweed (Ambrosia psilostachya). This resembles short ragweed grossly but is perennial. A fair pollinator.

except on very windy days, and are therefore relatively unimportant. For this reason, the important plants are those which grow abundantly and produce in large quantities pollen of a kind that can be held in the air for a considerable period of time.

The amount of pollen in the air during a pollen season varies with certain weather conditions. Large quantities of pollen can be dislodged by wind and carried for considerable distances. The quantity of pollen in the air varies not only with wind but also with other weather conditions. For instance, on cloudy days the

pollination of plants carried into our greenhouses practically ceases, and cloudy weeks are associated with periods of marked relief for patients who are sufferers from hay fever. When at the end of cloudy periods the sun comes out brightly, pollination of the plants becomes profuse and symptoms recur in patients who had previously been almost well. Sunny, dry spells occasionally dry up the plants so that the pollen season is cut short just as effectively as it is by an early frost. Consequently, observations concerning the date of

Fig. 10.—Burweed marsh elder (Iva xanthiifolia). Less abundantly distributed than the two prominent members of the ragweed group. It pollinates abundantly.

onset and duration of the pollen seasons vary somewhat from year to year. It may be mentioned, further, that the commencement of a pollen season does not correspond with the beginning of symptoms in hay fever patients. Very often pollination antedates clinical hay fever by two weeks or more. Symptoms commence apparently not at the beginning of the pollen season but at a time when pollen is produced and distributed in the air in certain abundance.

Writers on this subject agree in dividing seasonal cases into

Fig. 11.—Marsh elder (Iva ciliata). Uncommon except in marshy land. A good pollinator.

Fig. 12.—Cocklebur (Xanthium commune). Most common in fields and gardens recently cultivated. A good pollinator.

Fig. 13.—Pigweed (Amaranthus retroflexus). Common in cultivated grounds. A fair pollinator.

Fig. 14.—Lamb's-quarter (Chenopodium album). Common in cultivated places; almost as common as ragweed. Pollinates profusely.

three groups: The early spring cases, which occur coincident with pollination of the trees; the late spring and early summer cases, which occur with pollination of the grasses, and the fall cases, which accompany pollination of the weeds. In addition to this there are, of course, combined cases in which the patient is sensitive to two or more groups of flora and suffers over a more prolonged season. Also, persons sensitive to some of the earlier pollinators (such as lamb's-quarter) may suffer over a prolonged

Fig. 15.—False Ragweed (Franseria tenuifolia) (Gaertneria tenuifolia). This ragweed resembles Western ragweed very closely except that the fruit has spines.

season owing to the cutting followed by a second growth of some of the plants.

It is not possible in a paper of this scope to describe all the plants found in this district. The discussion must be restricted, for the sake of brevity, to the common producers of light pollen.

Of the trees, those which are numerous and rather generally distributed and produce pollen in quantity are box elder, sycamore, cottonwood, ash, hazelnut, black walnut, hickory and oak. Each pollinates for about three weeks in periods running between March and June. Most of them pollinate abundantly in the latter part

of April and early part of May. Soft maple is the first to pollinate, and black walnut is the latest. Trees that occur less generally are the tree of heaven, hard maple, silver poplar, hackberry, alder, birch, ironwood, Scotch pine, Austrian pine and chestnut. Any of the foregoing are possible sources of early spring hay fever or asthma.

Of the grasses, the following are very generally distributed, grow luxuriantly and produce light pollen in abundance: rye, blue grass, timothy, slough grass and orchard grass. Their dates of pollination run from the middle or latter part of May, through June, and

Fig. 16.—Spiny amaranth (Amaranthus spinosus). One of the careless weed group. Grows only in rich soil. A good pollinator.

include, as a rule, one or two weeks in July. Sudan grass and Johnson grass are not very abundant in this district, and produce a very heavy pollen. They pollinate, however, over a long period, running through the summer and fall months. The less common grasses are sorghum, big bluestem, foxtail, millet, marsh grass, redtop, wild rye, barnyard grass, gama grass, wheat grass, and Indian grass. The cultivated grains, such as wheat and corn, are relatively unimportant from the standpoint of pollen allergy, because of the facts that their pollen is either produced in relatively

small quantity or is too heavy to be carried for any great distance by wind.

Of the weeds that pollinate during the fall months, the following are generally distributed, grow profusely, and produce pollen in quantity: small ragweed, giant ragweed, marsh elder, cocklebur, the pigweeds, spiny Amaranth, water hemp, lamb's-quarter, red sorrel, hop, and hemp. The small ragweed grows in greatest abundance. The giant ragweed is the greatest producer of pollen. These two weeds, as pollen producers, rank far ahead of other weeds in

Fig. 17.—Western water hemp (Acnida tamariscina). The large plant on the left is the male plant. It produces large quantities of light dry pollen. The small plant on the right is female and produces no pollen whatever. Common in cultivated moist fields.

this district. Other weeds that are good pollinators but relatively scarce as compared with the foregoing are burweed marsh elder, southern ragweed, western ragweed, Russian thistle, wormwood, and firebush. The dates of pollination run from the latter part of July until frost. The great majority do not pollinate abundantly before the first week in August. Practically the entire group pollinate during the latter part of August and through September. Pollen is produced most abundantly by the majority of the weeds

in the latter week of August and through September, and during this period the great majority of the weeds mentioned pollinate profusely. Lamb's-quarter, Sudan grass, and Johnson grass differ from most plants in having a very long season. Each may run from June until frost, and in each case the date of pollination is affected by cutting. This is often followed by a second growth and a second season of profuse pollination.

It becomes apparent from a comparison of botanic observations with the results of specific testing that plants which produce the

Fig. 18.—Prairie sage (Artemisia ludoviciana). One of the many perennial species of wormwood. A good pollinator.

greatest quantity of pollen over the longest season are the most important factors in the causation of illness. For example, it can be observed that the tree season is relatively short for any given tree, that the number of trees of any given variety is relatively small as compared with the grasses and weeds, and that for this reason the quantity of pollen set free each year by any given variety of tree is not so great. In harmony with this, we find as a result of skin testing that persons sensitive to tree pollen are relatively rare.

Fig. 19.—Annual sage (Artemisia annua). Usually a weed but occasionally cultivated as sweet fern. Produces much more pollen than the perennial wormwoods.

Fig. 20.—Goldenrod. A conspicuous plant in many districts. It produces very little pollen and even this is difficult to dislodge from the plant. It is rarely a factor in the causation of pollen disease.

It may be mentioned, further, that the grass season is longer than the tree season and that the growth of the grasses, though more profuse than that of the trees, is not so profuse as the weeds. The quantity of grass pollen set free each year, therefore, stands between that of the trees and that of the weeds. In harmony with this, it is found that grass cases are much more common than the tree cases, but not so common as the weed cases.

The fall weeds are the greatest of all pollinators. They are general in distribution, profuse in growth, and produce light pollen

Fig. 21.—Buckhorn, or (English Plantain) (Plantago lanceolata). A spring weed which tends to grow on lawns. Its pollen is abundant, light, and dry.

in quantity over a long season. In harmony with this, we find by specific tests that fall weeds are by far the most common sources of pollen allergy in this district and, further, that of the weeds the two ragweeds that are the greatest producers of pollen are the commonest sources of illness.

The illness in either of the foregoing groups of cases may be very severe while it lasts; in fact, the most intensely sensitive pollen case that we have observed was a tree case in which the patient actually gave a severe constitutional reaction which required epinephrin,

after application of a small quantity of oak pollen to a scratch on the skin.

In Table I are mentioned the plants of this district that are the more important producers of pollen, arranged chronologically according to their date of pollination. Each x mark represents one week in time. The more important producers of pollen are underlined, as are also the weeks at which their pollen is produced in greatest quality. In the same table are given the results of skin tests obtained by a tabulation of 100 consecutive

Fig. 22.—Red sorrel (Rumex acetosella). A very early spring weed. It blooms coincident with some of the trees, especially the oaks. Male plant is on left, female on right.

cases tested as a routine with all the pollens mentioned. The majority of the tests were made by injecting intracutaneously 0.01 c.c. of a solution containing 0.01 mg. of pollen to a cubic centimeter. Reactions were called positive when there was an immediate appearance of a hive with pseudopods. Small reactions without pseudopods were called negative. The results of the ophthalmic, nasal, constitutional and therapeutic tests were not included in this table because these tests could not be carried out as a routine measure with all the pollens. The latter tests were made only with the

TABLE I

POLLEN CALENDAR FOR KANSAS CITY

| BOTANICAL NAME | POPULAR NAME | DATES OF POLLINATION | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | MARCH | APRIL | MAY | JUNE | JULY | AUGUST | SEPTEMBER | FROST |
| Corylus americana | Hazelnut | x x | | | | | | | |
| Populus virginiana | Cottonwood | ....... | x x | | | | | | |
| Betula populifolia | Birch | ....... | x x x | | | | | | |
| Acer negundo | Box Elder | ....... | x x x | | | | | | |
| Ostrya virginiana | Ironwood | ....... | x x | x | | | | | |
| Quercus spp. | Oak | ....... | x | x x x | | | | | |
| Platanus occidentalis | Sycamore | ....... | x | x x | | | | | |
| Fraxinus americana | Ash | ....... | x x | x | | | | | |
| Hicoria spp. | Hickory | ....... | ....... | x x x | | | | | |
| Juglans nigra | Black Walnut | ...... | ....... | x x x x | x | | | | |
| Rumex acetosella | Red Sorrel | ....... | ....... | x x x | x x x x | | | | |
| Secale cereale | Rye | ....... | ....... | x x | x | | | | |
| Poa pratensis | Blue Grass | ....... | ....... | x x | x x x x | | | | |
| Dactylis glomerata | Orchard Grass | ....... | ....... | x | x x x x | | | | |
| Chenopodium album | Lamb's-Quarter | ....... | ....... | ....... | x x x x | x x x x | x x x x | x x x x | frost |
| Phleum pratense | Timothy | ....... | ....... | ...... | x x x x | x x | | | |
| Plantago lanceolata | English Plantain | ....... | ....... | x x | x x x x | x x x | | | |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Tripsacum dactyloides | Gama Grass | . . . . . . | . . . . . . | . . . . . . | x x x x | | | | |
| Agrostis palustris | Redtop | . . . . . . | . . . . . . | . . . . . . | x x | x | | | |
| Sorghum sudanensis | Sudan Grass | . . . . . . | . . . . . . | . . . . . . | x x | x x x x | x x x x | x x x x | frost |
| Amaranthus spinosus | Spiny Amaranth | . . . . . . | . . . . . . | . . . . . . | x | x x x x | x x x x | x x x x | frost |
| Acnida tamariscina | Water Hemp | . . . . . . | . . . . . . | . . . . . . | . . . . . . | x x | x x x x | x x | |
| Cannabis sativa | Hemp | . . . . . . | . . . . . . | . . . . . . | . . . . . . | x | x x x x | x x x x | frost |
| Ambrosia trifida | Giant Ragweed | . . . . . . | . . . . . . | . . . . . . | . . . . . . | . . . . . . | x x x x | x x x x | frost |
| Amaranthus retroflexus | Redroot Pigweed | . . . . . . | . . . . . . | . . . . . . | . . . . . . | x | x x x x | x x x x | frost |
| Humulus japonica | Japanese Hop | . . . . . . | . . . . . . | . . . . . . | . . . . . . | . . . . . . | x x x x | x x x x | frost |
| Xanthium commune | Cocklebur | . . . . . . | . . . . . . | . . . . . . | . . . . . . | . . . . . . | x x x | x x x | |
| Ambrosia elatior | Short Ragweed | . . . . . . | . . . . . . | . . . . . . | . . . . . . | . . . . . . | x x | x x x x | |
| Ambrosia bidentata | Southern Ragweed | . . . . . . | . . . . . . | . . . . . . | . . . . . . | . . . . . . | x x | x | |
| Ambrosia psilostachya | Western Ragweed | . . . . . . | . . . . . . | . . . . . . | . . . . . . | . . . . . . | x x x | x x x | |
| Iva ciliata | Marsh Elder | . . . . . . | . . . . . . | . . . . . . | . . . . . . | . . . . . . | x | x x | |
| Iva xanthiifolia | Burweed Marsh Elder | . . . . . . | . . . . . . | . . . . . . | . . . . . . | . . . . . . | . . . . . . | x x x x | |
| Bidens involucrata | Marsh Marigold | . . . . . . | . . . . . . | . . . . . . | . . . . . . | . . . . . . | . . . . . . | x x x x | |
| Artemisia ludoviciana | Prairie Sage, Wormwood | . . . . . . | . . . . . . | . . . . . . | . . . . . . | . . . . . . | . . . . . . | x x x | |
| Artemisia annua | Annual Sage | . . . . . . | . . . . . . | . . . . . . | . . . . . . | . . . . . . | . . . . . . | x x | |

The plants are arranged chronologically, allowing four weeks to the month. Each x mark represents one week and the weeks underlined show the period of heaviest pollination.

pollen solutions which gave the stronger skin reactions or which were suspected for other reasons as causes of illness.

The great majority of patients show skin sensitiveness to a large number of pollens, often to each member of certain groups of pollens. As a general rule, the pollen that gives the strongest skin test is the one that gives a positive conjunctival test when sprayed into the eye in a dilution of 1:1000. The other pollens which give less intensive skin tests, usually give negative conjunctival tests. The pollens that have given positive conjunctival tests have usually been the ones we thought responsible for symptoms, and for this

Fig. 23.—Hemp (Cannabis sativa). A common lowland weed having separate male and female plants. An abundant pollinator.

reason were chosen for therapy. Usually, therapy with these pollens (from one to four in number) gave complete clinical relief.

The foregoing statements are subject to marked exception. Occasionally it seemed that when patients were sensitive to a number of pollens they were made ill, not by any individual member of the group, but rather by the combined action of several or all of them. Furthermore, some patients who gave flatly negative conjunctival tests to each individual member of the group of pollens to which they

gave strong positive skin tests occasionally reacted strongly when a mixture of the pollens was sprayed into the conjunctival sac or nose. We observed several instances in which the patient was actually made ill by exposure to pollen of air which did not include the one pollen to which they reacted most markedly when tested by skin and conjunctival tests. For example, one season a few patients, sensitive chiefly to *Ambrosia elatior*, continued to have hay fever after *Ambrosia elatior* had ceased pollinating, because of a spell of sunny, dry weather which apparently burned it up. The

Fig. 24.—Japanese hop (Humulus japonica). Often found with its relative, hemp, in moist wastes. Produces dry pollen in abundance.

symptoms in these patients must have been kept going by other pollens to which they were less sensitive than to *Ambrosia elatior*.

Specificity is an interesting and marked characteristic of sensitiveness to pollen. Patients sensitive to ragweed in one locality may be unaffected by ragweed pollen in other districts. At the same time, specificity in some cases seems to be largely a matter of degree of sensitiveness, that is, the pollen which causes the patient to have hay fever is not necessarily the pollen to which he is most sensitive, but the one which he gets in greatest dosage. In other

Fig. 25.—Russian thistle (Salsola pestifer). Grows in dry or sandy soil. A good pollinator.

Fig. 26.—Orchard grass (Dactylis glomerata). Common in vacant lots and along road sides. Thrives in the shade. An abundant producer of dry pollen.

Fig. 27.—Timothy (Phleum pratense). Grows in meadows, fields and along roadsides. One of the most common grasses. Pollinates profusely.

Fig. 28.—Blue grass, June grass (Poa pratensis). A widely distributed grass and a good producer of pollen.

Fig. 29.—Rye (Secale cereale). A good producer of pollen.

Fig. 30.—Bermuda grass (Capriola dactylon). Found chiefly in the south and southwest. A good pollinator in dry hot climates.

Fig. 31.—Johnson grass (Holcus halepensis). An abundantly distributed grass in the south. The pollen, however, is large, heavy, and not abundant. The annual form, Sudan grass (holcus sorghum sudanensis) is cultivated for forage purposes. It is a heavy pollinator but the pollen produced is almost as large and heavy as corn pollen. It would seem to be rarely a factor in the causation of pollen disease.

Fig. 32.—Corn (Zea mays). A good producer of large heavy moist pollen granules. Because of its weight, corn pollen is not carried far by wind and is, therefore, a factor in pollen disease only for individuals who come in close contact with the plants.

Fig. 33.—Bloom of box elder (Acer negundo). A common shade tree which produces a large quantity of relatively light pollen. The illustration shows the male blossoms and young leaves.

Fig 34.—Ash (Fraxinus americana). A common street and yard tree. The male blossoms shown are composed entirely of bare anthers. They appear before the leaves and produce an enormous amount of pollen.

Fig. 35.—Paper birch (Betula papyrifera). A much used decorative tree. Illustration shows the male blossoms.

Fig. 36.—Sycamore (Platanus occidentalis). A common street tree. The larger balls are male and when mature, drop off. The small balls later develop into the familiar button ball containing the seed.

words, symptoms seem to be the result of a mean between degree of sensitiveness and dose of pollen encountered.

It is interesting to mention at this point that, of the patients who were clinically sensitive to pollen, 45 per cent reacted positively to some other substance, either vegetable, fruit, grain, sea food or animal dander.

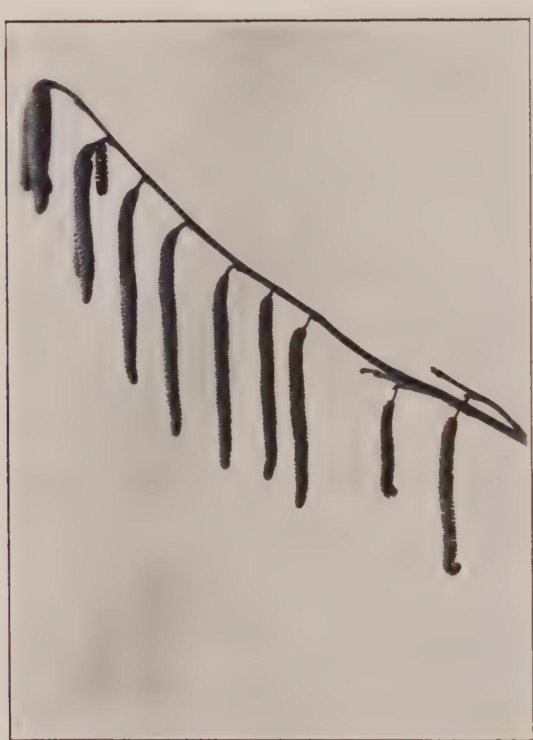

Fig. 37.—Hazelnut (Corylus americana). The earliest abundant pollinator. It pollinates frequently before the snow melts.

It is interesting, also, to mention that a very few patients who were sensitive to pollen reacted also to some other part of a plant, either of the same or of a different family. For example, one patient sensitive to oak pollen reacted markedly to oak tree juice. One *Ambrosia elatior* patient reacted both by skin test and by inhalation test to an extract of the leaves of blue grass but not to blue grass pollen; several reacted to extracts from the leaves or blossoms of white or red clover, one to timothy extract, and one to straw.

Occasionally pollen sensitive cases are sensitive to the action of physical agents, as will be described subsequently. It was found also that fall weed cases which continue to have symptoms during the winter months are frequently heat sensitive and have their symptoms as a result of frequent changes from cold to heat.

Fig. 38.—Scotch pine (Pinus sylvestris). Much used as an ornamental tree. A very abundant pollinator.

### Summary

In Table II are given the names of the commoner anemophilous plants in and around Kansas City, Mo. The relative abundance in distribution of the plants is represented by 1 to 4 x marks. The relative abundance of the pollen produced by each is also represented by 1 to 4 x marks. The weight per c.c. of dry pollen, the diameter of the granules, the character of the pollen and habitat of the plants are also given.

By reviewing the table, one can see that the following plants are the greatest producers of light pollen in this district, and would seem, therefore, from a botanic standpoint, to be the more important agents in the causation of pollen allergy. They are given in the order of their relative importance:

*Weeds.*—Short ragweed, giant ragweed, marsh elder, cocklebur, lamb's-quarter, water hemp, and the amaranths.

*Grasses.*—Timothy, blue grass, and orchard grass.

*Trees.*—Hickory, oak, black walnut, cottonwood, and box elder.

It is interesting to note how closely the botanic data harmonize

TABLE II

POLLEN SURVEY, KANSAS CITY, MO.

| POPULAR NAME | BOTANICAL NAME | ABUNDANCE OF PLANTS | ABUNDANCE OF POLLEN | WEIGHT IN GRAMS PER C.C. VOLUME OF POLLEN | DIAMETER OF POLLEN IN MICRONS | CHARACTER OF POLLEN AT MATURITY | HABITAT |
|---|---|---|---|---|---|---|---|
| Tree of Heaven | Ailanthus glandulosa | x | x x | | | Moist | Yards. Male and female. Spreads rapidly. |
| Box Elder | Acer violacea | x x | x x x | .53 | 38 | Moist | Along streams, and in yards. Male and female. |
| Hard Maple | Acer nigrum | x | x | | 52 | Dry | Woods. Other spp. used for streets. |
| Soft Maple | Acer saccharinum | x x | x | | 44 | Dry | Woods and yards. |
| Sycamore | Platanus occidentalis | x x | x x x | .47 | 19 | Dry | Streets and woods. |
| Cottonwood | Populus virginiana | x x x | x x x | .46 | 28 | Resinous | Woods, wastes, yards. Male and female. |
| Ash | Fraxinus americana | x x | x x x x | .55 | 27 | Dry | Woods and streets. Male and female |
| Hazelnut | Corylus americana | x x | x x x x | .62 | 24 | Dry | Woods. A shrub. |
| Filbert | Corylus avellana | x | x x x x | | 28 | Dry | Parks. Cultivated shrub. |
| Hackberry | Celtis occidentalis | x x | x | | | Moist | Woods. |
| Alder | Alnus glutinosa | x | x x x | .36 | 27 | Resinous | Yards. |
| Black Walnut | Juglans nigra | x x x | x x x | .61 | 38 | Dry | Woods. |
| Hickory | Hicoria spp. | x x x | x x x | .61 | 40-48 | Dry | Woods. |
| Birch | Betula populifolia | x | x x x | .40 | 25 | Dry | A decorative yard tree. |
| Ironwood | Ostrya virginiana | x x | x x x | .63 | 26 | Dry | Woods. |
| Oak | Quercus spp. | x x x | x x x | .65 | 36-40 | Dry | Woods. Nine varieties listed. |
| Scotch Pine | Pinus sylvestris | x | x x x x | .32 | 45 | Dry | Parks. |
| Austrian Pine | Pinus austriaca | x | x x x x | .28 | 52 | Dry | Parks. |
| Mulberry | Morus alba | x | x x | . | 22 | Dry | Woods. Male and female. |
| Johnson Grass | Sorghum halapense | x | x x x | | 45 | Dry | Rare in North Mo. |
| Sudan Grass | Sorghum sudanensis | x x | x x x | .69 | 50 | Moist | Much planted for forage. |
| Sorghum | Sorghum saccharum | x | x x | | | Moist | Planted. |
| Rye | Secale cereale | x x | x x x | .50 | 55 | Moist | Field crop. |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Blue Grass | Poa pratensis | x x x x | x x | .44 | 33 | Dry | Lawns, roadsides, pastures. |
| Timothy | Phleum pratense | x x x | x x x | .64 | 40 | Dry | Fields, wastes, roadsides. |
| Big Bluestem | Andropogon furcatus | x x | x x | | 44 | Dry | Prairies |
| Foxtail | Setaria glaucus et viridis | x x x | x | | 42 | Dry | Wastes. |
| Millet | Setaria germanica | x | x | .30 | 30 | Dry | Field crop. |
| Marsh Grass | Spartina cynosuroides | x | x x | | 41 | Dry | Moist lowland. |
| Gama Grass | Tripsacum dactyloides | x x | x x x | .65 | 53 | Dry | Moist fields and wastes. |
| Wheat | Triticum aestivum | x x | x | | | Dry | Field crop. |
| Wheat Grass | Agropyron smithii | x | x x | .41 | 42 | Dry | Prairie. |
| Orchard Grass | Dactylis glomerata | x x | x x x | .59 | 36 | Dry | Lawns. Thrives in shade. |
| Corn | Zea mays | x x x | x x x x | .71 | 90 | Moist | Field crop. |
| Redtop | Agrostis palustris | x x | x x | | 30 | Dry | Moist fields. |
| Purple-top | Tricuspis seslerioides | x x | x | | | Dry | Prairies. |
| Wild Rye | Elymus glaucifolius | x x | x | | 48 | Dry | Wastes. |
| Barnyard Grass | Panicum crus-galli | x x | x | | | Dry | Moist wastes. |
| Indian Grass | Sorghastrum nutans | x | x x | | 45 | Dry | Prairies. |
| Pigweed, Redroot | Amaranthus retroflexus | x x | x | .53 | 24 | Dry | Gardens. Cultivated wastes. |
| Slender Pigweed | Amaranthus hybridus | x x x | x x | .56 | 26 | Dry | Gardens. Cultivated wastes. |
| Spiny Amaranth | Amaranthus spinosus | x x | x x x | .57 | 28 | Dry | Rich wastes, cattle yards. |
| Water Hemp | Acnida tamariscina | x x x | x x x x | .60 | 24 | Dry | Moist cultivated land. |
| Lambs-quarter | Chenopodium album | x x x | x x x | .56 | 27 | Dry | Gardens, rich wastes. |
| Wormseed | Chenopodium ambrosioides | x x | x | | | Dry | Rich wastes. |
| Russian Thistle | Salsola pestifer | x | x | .53 | 25 | Dry | Sandy or clay wastes. |
| Summer Cypress | Kochia spp. | x x | x | | 36 | Dry | Sandy wastes. |
| Orache | Atriplex spp. | x | x | | | Dry | Cultivated wastes. |

TABLE II—CONT'D

POLLEN SURVEY, KANSAS CITY, MO.

| POPULAR NAME | BOTANICAL NAME | ABUNDANCE OF PLANTS | ABUNDANCE OF POLLEN | WEIGHT IN GRAMS PER C.C. VOLUME OF POLLEN | DIAMETER OF POLLEN IN MICRONS | CHARACTER OF POLLEN AT MATURITY | HABITAT |
|---|---|---|---|---|---|---|---|
| Short Ragweed | Ambrosia elatior | x x x x x | x x x x | .30 | 22 | Dry | Waste land. Our most frequent weed. |
| Giant Ragweed | Ambrosia trifida | x x x x | x x x x x | .30 | 18 | Dry | Moist wastes. |
| Southern Ragweed | Ambrosia bidentata | x x | x x x x | .31 | 24 | Dry | Dry rocky soil. |
| Western Ragweed | Ambrosia psilostachya | x | x x x | .47 | 24 | Dry | Prairies. |
| Marsh Elder | Iva ciliata | x x | x x x | .32 | 27 | Dry | Low rich land. |
| Burweed Marsh Elder | Iva xanthiifolia | x x | x x x x | .35 | 20 | Dry | Wastes. Western and northwestern states. |
| Cocklebur | Xanthium commune | x x x | x x x | .33 | 28 | Dry | Rich wastes. |
| Marsh Marigold | Bidens involucrata | x x x | x x | .37 | 36 | Oily | Marshes. |
| Goldenrod | Solidago spp. | x x | x | .35 | 25 | Oily | Prairies. |
| Sunflower | Helianthus spp. | x x x | x x x | .34 | 35 | Resinous | Cultivated land, wastes. |
| Yellow Weed | Amphiachyris dracunculoides | x | x x | | 20 | Resinous | Prairies. |
| Hop, Japanese | Humulus japonica | x x | x x x x | .55 | 25 | Dry | An escape. Wastes. |
| Hemp | Cannabis sativa | x x x | x x x x | .51 | 24 | Dry | Moist wastes. |
| Buckhorn | Plantago lanceolata | x x x | x x | .57 | 26 | Dry | Lawns and roadsides. |
| Castor Bean | Ricinus | x | x x | .45 | 40 | Dry | Planted in yards. |
| Cat-tail | Typha latifolia | | x x x x x | | 30 | Dry | Marshes. |
| Mugwort | Artemisia ludoviciana | x | x x x | .55 | 25 | Dry | Prairies. |
| Annual Sage | Artemisia annua | x | x x x x | | 23 | Dry | Wastes. |
| Red Sorrel | Rumex acetosella | x x | x x x | .38 | 25 | Dry | Prairies. Only on sour land. |
| Tall Dock | Rumex Mexicanus | x x x | x | | 27 | Dry | Wastes. Only on sour land. |

Fig. 39.—Kingnut (Hicoria lacinosa). A hickory. Is closely related to the walnuts. Pollinates abundantly.

Fig. 40.—Cottonwood (Populus virginiana). A very common tree in the central states. Photograph shows the male blossoms which produce pollen in great abundance. The female tree is conspicuous for the shedding of cotton but produces no pollen.

Fig. 41.—Sweet Gum (Liquidambar). Common in the south. The erect blossoms are the male and produce pollen. The pendant blossoms are female and produce no pollen.

Fig. 42.—Bur oak (Quercus macrocarpa). This is an example of the eight varieties of oak common in the Mississippi valley. It is a widely distributed tree. Male blossoms appear as the leaves unfold, mature, and liberate a large amount of pollen. Its seasons vary with the different varieties and for all varieties, lasts about one month.

Fig. 43.—Pignut hickory (Hicoria minima). Found chiefly in parks and woods. Illustration shows young leaves and blossoms.

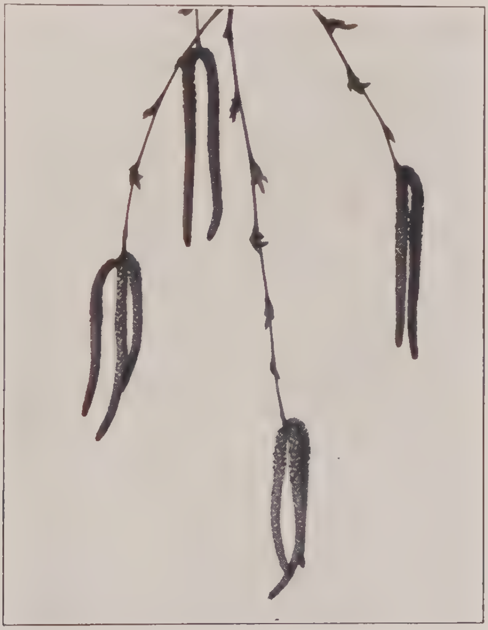

Fig. 44.—Red birch (Betula nigra). A decorative tree. Illustration shows young blossoms.

Fig. 45.—Greenhouses built for the collection of pollen. Plants are carried into the greenhouses and put in troughs containing water. The blossoms are allowed to hang over glazed paper. Under the influence of sunlight and occasional shaking, the pollen falls on the paper and can be collected in large amounts.

Fig. 46.—Plants in troughs in a greenhouse which, in quantities such as this, should yield fifty to two hundred grams of pollen within a period of two or three days. It illustrates how great is the quantity of pollen liberated in the air at the height of the season on windy sunny days. Pollen collected in this way should be dried within a period of two or three days in an oven at a temperature not exceeding 45° C. When dry, it should be sifted through a fine copper mesh seive and kept in air tight containers. Pollen can be kept in this way for years.

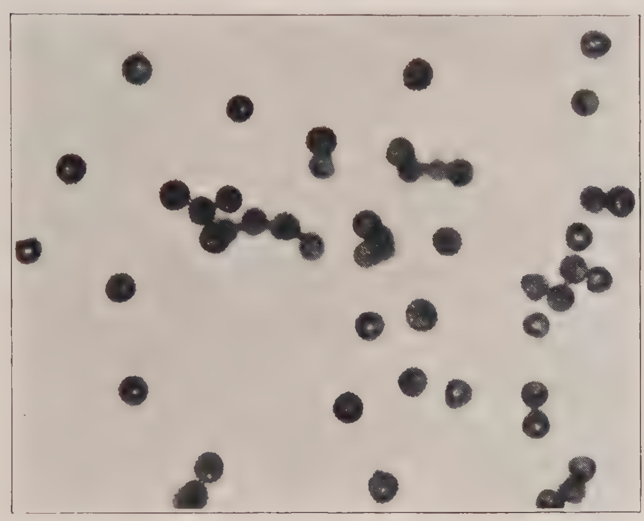

Fig. 47.—Ragweed pollen. Small, round, spiculated. This type characterizes the entire Ambrosaciae group. This includes the ragweeds, false ragweeds, cocklebur, and marsh elders. The pollen of the different species varies in size.

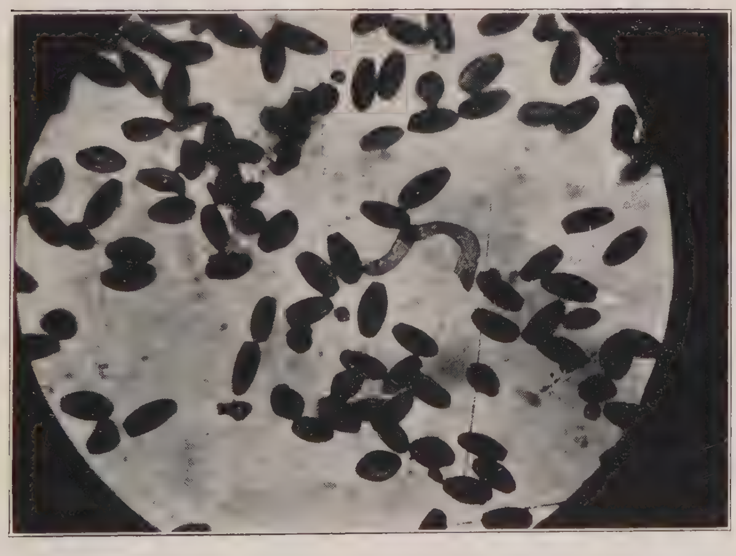

Fig. 48.—Pollen of soft maple. Larger than ragweed pollen, oval, nonspiculated. This characterizes the entire willow group, oak group, and maple group, including box elder. There is marked variety in the size, however, of these pollens (see Table II). The longitudinal line which makes the granule resemble a grain of wheat is characteristic of oval pollens. Flattened ends characterize a majority of them, especially the oaks, ash, and red sorrel. Irregularities in the shape of pollen granules are partly the result of drying.

Fig. 49.—Pollen of ash. This resembles the oval pollen shown in the previous illustration except for the fact that the ends are so flattened as to give it a different shape. This characterizes pollen of the oaks and ash group and red sorrel.

Fig. 50.—Pollen of lamb's-quarter. Small, round, and nonspiculated. This characterizes pollen of the amaranth and chenopod groups.

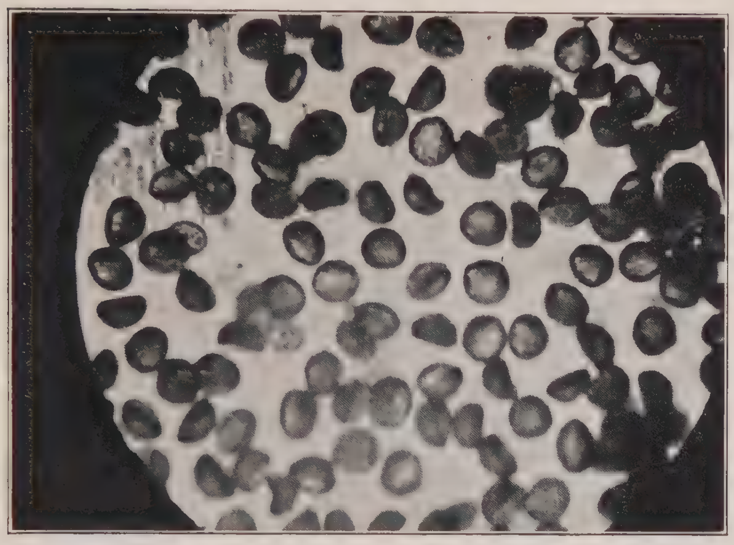

Fig. 51.—Walnut pollen. Large, smooth walled, partly collapsed spheres. This is also characteristic of hickory pollen. The collapsed shape of spheres such as these is frequently a result of drying. Many appear round when first shaken from the plant.

Fig. 52.—Pollen of corn. The largest pollen. A typical grass pollen though much larger than the average. Grass pollens are, as a class, smooth-walled, irregular spheres. The indentations which give rise to the irregular shapes are often a result of drying since grass pollen examined immediately after it is dislodged is often spherical. Grass pollens stain more deeply with iodine than other pollens.

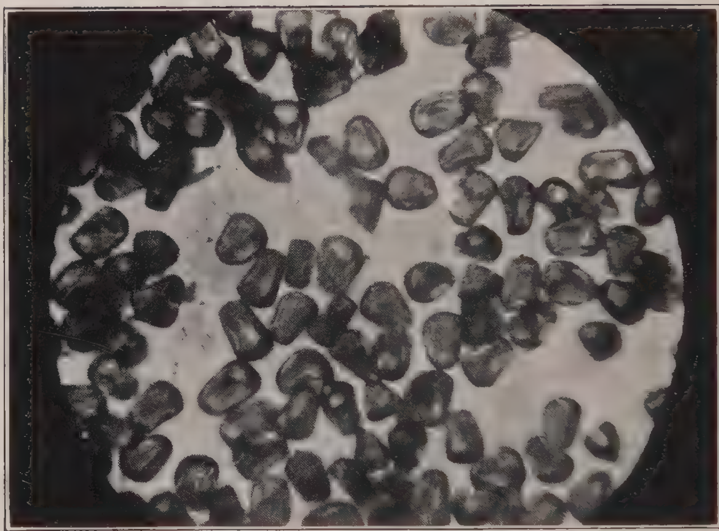

Fig. 53.—Pollen of slough grass. This has the same general characteristics of corn pollen except it is much smaller.

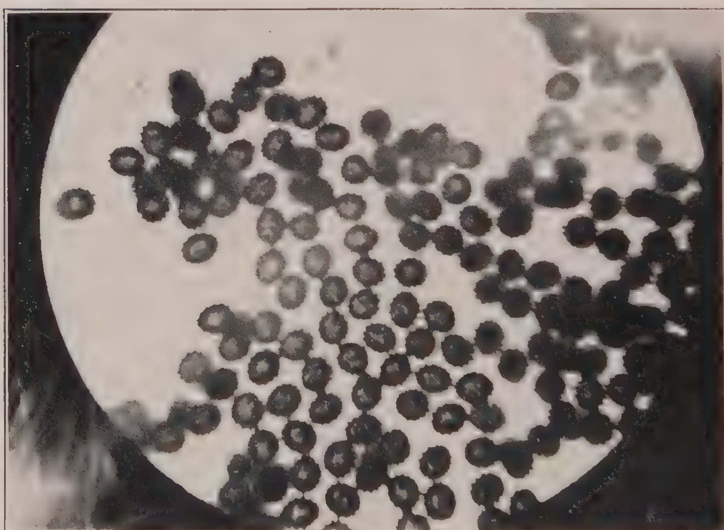

Fig. 54.—Goldenrod pollen. Larger than ragweed, spherical, coarsely spiculated. This characterizes pollen of the composite group. This includes sunflower, asters, daisies, and many other flowering plants. The spicules make the pollen difficult to dislodge.

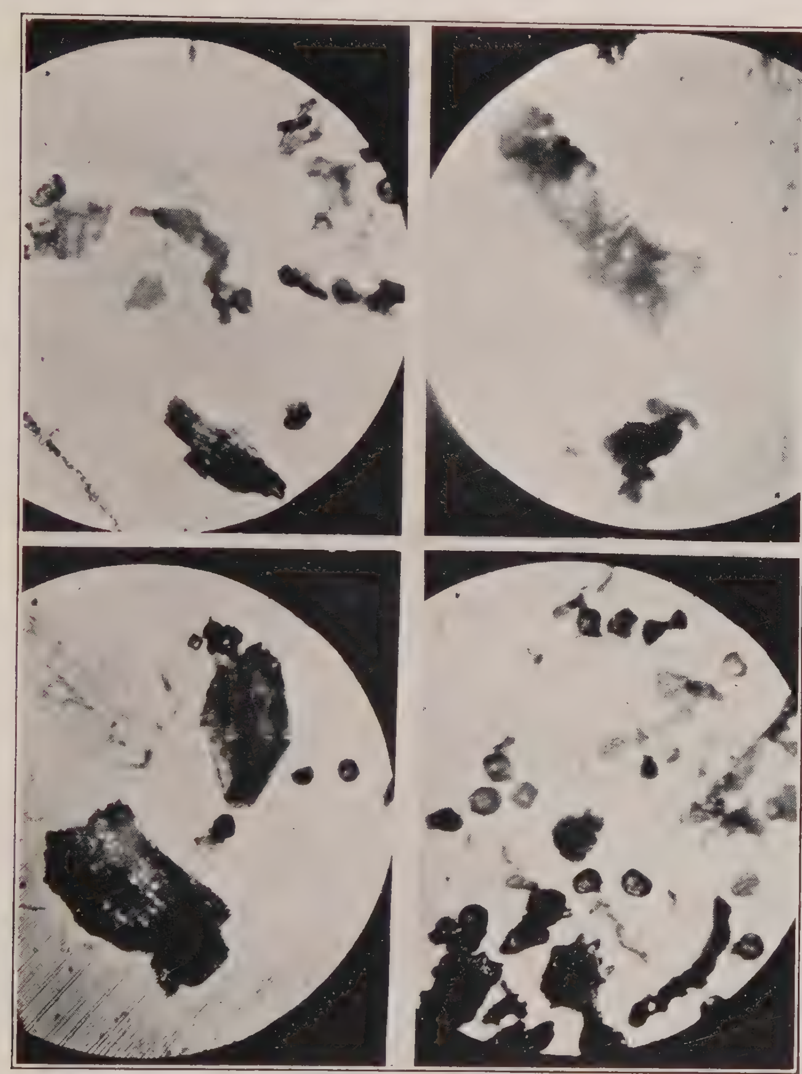

Fig. 55.—Examples of impure pollen. These are four of some twenty specimens examined which had been purchased by a friend. Each of the twenty specimens contained much more dust than pollen. This illustrates the need of microscopic examination of pollen before extracts are made. Extracts made from pollen of this sort could not be used successfully in therapy since the solutions would be too weak to be potent. The use of pollen of this sort accounts for many therapeutic failures.

Fig. 56.—Specimens of eighty varieties of wind-borne pollen collected within the city limits of Kansas City, Missouri.

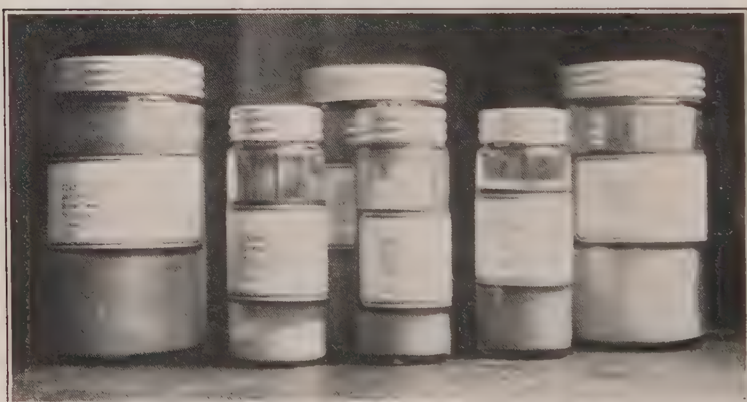

Fig. 57.—Specimens of pollen in quantity. It is not difficult with the help of a good botonist to collect the important pollens in quart lots. Pollen which is hard to collect is usually unimportant so far as pollen disease is concerned.

with the results obtained by specific testing. Of the pollen-sensitive patients, by far the greater number were sensitive to the light pollens set free in the air in the greatest abundance over the longest period of time; first and foremost, to short ragweed; secondly, to giant ragweed, and less often to cocklebur, marsh elder, lamb's-quarter, wormwood and water hemp. The latter weeds showed relatively large percentages so far as skin tests were concerned; but not nearly so great a proportion as this gave positive conjunctival tests, and we believed that patients were not so often made ill by these pollens in the amounts encountered naturally as the skin tests would indicate. The spring grasses, with their shorter season and smaller ratio of pollen production, did not compare in number of sensitive cases with fall weeds. Finally, the trees with their relatively short season and the comparative scarcity of any single variety were responsible for very few cases. In fact, we did not observe a sufficient number of tree cases to permit the drawing up of substantial statistics. So few patients were found sensitive to flowering plants and cultivated grains that these cases were put down as curiosities. It seemed quite clear that the principal offenders, both in number of cases and in the duration and severity of illness produced, were the weeds which produce the greatest quantity of pollen over the longest period of time.

Given a patient who inherits a constitution which permits him to become sensitive to pollen, he is most likely to react clinically to the one to which he is most intensely and most constantly exposed.

## CHAPTER XI

## PRIMARY CAUSES OF REACTION OTHER THAN POLLEN

### Sensitiveness to Emanations of Vegetable Origin

Patients may be sensitive not only to pollen, but to other parts of the plant, including the leaf, bloom, stem, or root. They may be sensitive to the plant in its natural state, or after it has been treated for commercial purposes, or both, or may be sensitive to almost innumerable elements derived from plant life, which are isolated in relatively pure state for commercial purposes. Sensitiveness of this type is not so common as pollen sensitiveness, and is rarely so intense.

It is not uncommon for patients to speak of reaction upon contact with roses and other flowers. Such patients are frequently insensitive to other agents. Their reaction could hardly be attributed to the pollen of the flower because flowering plants produce little pollen and this is usually adherent to the plant.

A small number of individuals sensitive to the grasses, such as timothy, blue grass, white clover, or red clover, give positive skin tests to extracts of the leaves or bloom, and react clinically upon contact with the plant weeks before the pollen season starts. An occasional patient reacts to dried grasses, even to straw matting used as a covering for floors. One very interesting patient had coryza, puffiness of the face, nasal reaction, cough, asthma, and prostration whenever he put on a Panama straw hat. He was not made ill by other types of straw or by other hats. An occasional case reacts to the woody matter of plants. Two patients of this type who were carpenters were sensitive respectively to birch wood and mahogany and reacted with dermatitis of the hands and face whenever they worked for several days with these woods. This type of case would seem analogous to those which react to the volatile oils and essential oils of plant origin. This is not uncommon. Laboratory workers are occasionally sensitive to cedar wood oil. In one case, sensitiveness to turpentine was so marked that exposure to fresh paint caused not only bronchial symptoms, but collapse

and abdominal distention which four times led to a diagnosis of intestinal obstruction and operation.

Sensitiveness to cotton seed and flax seed is interesting. Extracts of these two agents rather frequently give intensely positive skin tests. The patient may suffer from asthma when there is no apparent contact with either cotton seed or flax seed. It seems possible that cases of this sort might react to raw cotton or linen with which they come in contact, although I have never been able to convince myself that this is the case. One patient sensitive to flax seed gave an intensely positive skin reaction to an extract of flax linum used so commonly in the construction of houses.

Sensitiveness to orris is relatively common. Patients frequently react to it both clinically and cutaneously; in fact, more frequently to this than to any other single agent studied, except pollen. Orris is used extensively in the manufacture of perfumes and cosmetics—in fact, it is contained in the majority of perfumes, face powders, sachets, tooth pastes, tooth powders, and is even used occasionally as a flavoring material and as a dye. One patient relieved of chronic reaction through careful avoidance of orris had occasional abdominal attacks which were eventually traced to the eating of butterscotch pie in which orris was used as a flavor. He was apparently permanently relieved through its avoidance.

Sensitiveness to perfume is relatively common, and since perfumes are used so frequently in toilet articles, sachets, etc., it is a relatively frequent source of disorder. In an endeavor to study this type of reaction, patients were tested routinely for one year to a number of the essential oils used commonly in perfumes and flavoring materials by inhalation tests and often by scratch tests. The following were obtained and used through the courtesy of Mr. A. S. Barada of Barada & Page, Inc.: almond, hyacinth, anethol, fennel, rosemary, peppermint, jasmine, caraway, violet, heliotrope, lavender, lemon, jackrose, celery, eugenol, orange flower, peach, vanilla, and camphor. Strange to say, very few positive tests were obtained. This need not be wondered at, however, when one bears in mind the tremendous number of substances used in the manufacture of perfumes, and the difficulties encountered in testing patients for them all.

In discussing emanations of vegetable origin, it might be well to mention as a class, the various products obtained by the distil-

lation of wood and coal, many of which are capable of sensitizing. These substances are used extensively in the arts and sciences, as dyes, drugs, chemicals, solutions for extracting purposes, cleaning purposes, and for fuel and lighting. It can be easily seen that a complete discussion of this phase of the subject would be almost endless, and a mere mention of the fact that a patient can become sensitive to many of the almost innumerable products of this source should be sufficient. In an endeavor to determine how common this type of sensitiveness might be, I tested routinely for one year both by inhalation and scratch tests with crude carbolic and crude guaiacol, obtained as a by-product, respectively, from the distillation of coal and wood, to Wright's wood smoke, a by-product from the distillation of wood, and to drip oil and drip water, obtained as a by-product from the manufacture of gas; to a solution of gasoline smoke, coal smoke, wood smoke, and tobacco smoke, prepared by burning these materials in a clay pipe and with a vacuum pump drawing the smoke through a solution of 50 per cent alcohol. Only an occasional frank positive test was obtained. Testing with the various substances as encountered naturally and information gained through history and observations by the patient gave a greater number of positive results.

## Sensitiveness to Feathers and Animal Hair

Sensitiveness to animal hair and feathers is an important cause of reaction but is rare as compared with pollen sensitiveness. Patients may be sensitive to one animal or to several animals. They may be sensitive to the animal itself, its cured fur, or both. The same is true in the case of sensitiveness to fowl and feathers. Patients sensitive to animal emanations are often sensitive to pollen, foods, or to the action of physical agents. The patients observed were sensitive to animals and fowl in about the following order: horses, cattle, sheep, hogs, dogs, cats, rabbits, guinea pigs, mice, and to chickens, ducks, and geese. Horse sensitiveness was much the most frequent source of reaction.

Frequent exposure seems here to be a factor, just as frequent constant exposure seems to be a deciding factor in the development of pollen sensitiveness. An individual whose habits or occupation brings him in frequent contact with a given animal is more likely to become sensitive to it than to others which he meets with rarely.

Sensitiveness of this type may be either slight or intense. Symptoms may be, therefore, either mild or severe. In mild cases, they amount to little more than sneezing and itching of the eyelids. In intensely sensitive cases, however, severe reactions which may amount to shock may occur even upon slight contact. In one case, previously alluded to, reaction consisting of sneezing, asthma, redness of the skin, profound weakness, and shock started on two occasions when the patient was in the open air at least fifty yards from a zoo. Symptoms of general reaction, such as this, however, are rare unless the degree of sensitiveness is intense and exposure marked.

The symptoms most commonly observed are nasal and orbital, less often cough and bronchial asthma, and occasionally edema of the superficial tissues and dermatitis.

As previously mentioned, a patient may be sensitive to the animal or fowl and not sensitive to their cured fur or feathers. In this case, the illness is not a matter of great moment unless the habits or occupation of the patient brings him frequently in contact with the animal to which he reacts. When a person is sensitive to cured hair or feathers, the illness may be chronic and avoidance of cause may be, in this case, difficult. Hair and feathers of many varieties are used extensively in the manufacture of wearing apparel, upholstery, rugs, draperies, bedding, etc. For this reason, sensitiveness of this type is frequently responsible for the so-called "house asthma."

When a patient is sensitive to an animal or fowl and not to the pelt, the patient usually visits a doctor's office with a correct diagnosis of his own case. Reactions in this type of case are usually prompt and definite and for this reason, the discovery of a relationship between exposure and reaction is simple. In the case of sensitiveness to cured fur or feathers, however, the reactions are often neither marked nor prompt and since fur and feathers are not objects so conspicuous as animals or fowl, the relationship between exposure and onset of illness may not be apparent and the mysteries of the illness may be difficult to unravel.

Sensitization tests with extracts of animal hair and feathers are often satisfactory although less often than in case of pollen sensitiveness.

A patient sensitive to one type of dander usually reacts cutaneously to it and to several others although they may be clinically sensitive to one animal only. Patients sensitive to horse dander usually react with almost equal positiveness to burro hair.

Strange to say, sensitiveness to wool or, at least, cutaneous sensitiveness to wool, is rare. Kahn, however, thinks that wool is a common cause of perennial asthma. This view would seem theoretically correct because of frequent contact of the respiratory membranes with traces of wool. One might possibly explain the failure of the skin to react on an assumption that frequent gross contact of the skin with wool would give rise to local cutaneous immunity. In my experience, wool sensitiveness has been extremely difficult to prove except in five cases of dermatitis caused by woolen underwear. I have obtained a frank positive skin reaction with pseudopods upon testing with wool extract in only one case of asthma.

The best treatment for sensitiveness to animal hair or feathers lies in avoidance of cause. Specific protein therapy is not justified except in the case of wool sensitiveness or in the case of patients whose habits necessarily bring them into frequent intimate contact with substances to which they react.

## Smoke

Normal individuals are affected in mild grade by the irritating effects of smoke. Many patients with nasal or bronchial reaction due to other causes are made worse by the nonspecific irritating effects of smoke and other vapors. In addition to this, however, certain patients are specifically hypersensitive to smoke and not to other agents. They may react to one or to several varieties of smoke. In a number of cases, reaction was traced definitely to hypersensitiveness to one or more of the following varieties: namely, wood smoke, coal smoke, gasoline smoke, smoke from gas stove, smoke from coal oil stove, tobacco smoke, cigar smoke (not cigarette smoke), the smoke of burning matches, and the smoke of frying grease. One patient was so sensitive to cigar smoke that she could not associate with individuals who were accustomed to smoke cigars. She was unaffected by cigarette smoke.

CASE 1.—*House Asthma Caused by Sensitiveness to Wood Smoke.*—The most marked example of this sort was that of a woman, age thirty-four, with family

history of asthma, who noticed that she had asthma in certain houses and in certain localities. The patient was a close observer and upon questioning, traced her illness to cities as compared with country districts and to houses heated with open fires or furnaces in contrast with those heated by steam. Her illness started soon after exposure to smoke generated by a burning coal shed close to her window.

She gave negative skin tests to the common foods and air-borne agents. She was finally tested by the application of a drop of Wright's wood smoke applied to a scarified area on the skin. A wheal 5 cm. in length appeared within a few moments followed by coryza, severe asthma, generalized erythema, and itching which necessitated the hasty use of adrenalin. At a later time inhalation tests made with a solution of Wright's wood smoke gave a frank positive reaction.

This patient proved so sensitive to wood smoke that she was actually affected by the traces of smoke adherent to draperies, rugs, upholstery, etc., in houses heated by open wood fires, even if a wood fire had not been used in the house for months.

Patients vary from time to time in their reaction to smoke. Furthermore, skin tests made with solutions prepared by passing the various smokes and vapors through a liquid, usually give negative reactions. These factors can be easily accounted for theoretically. Smoke must contain an enormous number of chemical bodies. The constituents of smoke must vary greatly, not only because of differences in material used as fuel, but also because of conditions of aeration and moisture which affect the rate and completeness of combustion. Since patients might become sensitive to a rare constituent of a certain type of smoke or a constituent common to many types of smoke, one could easily realize that this group of cases would vary in their symptomatology according to their type of sensitiveness and the type of exposure and would fail to react to smoke of certain varieties unless generated under conditions favorable for the elaboration of the product to which they react. It may be repeated that one patient excessively sensitive to cigar smoke was unaffected by cigarette smoke.

Pollen cases are frequently made worse by smoke during the pollen season. At other times they may tolerate smoke relatively well. Patients sensitive to the action of physical agents to be described subsequently often react to smoke. It is difficult to determine whether cases of this variety are true cases of multiple sensitization and react to the combined effect of the two agents or whether smoke in their cases acts simply as a nonspecific irritant. I believe both varieties of case exist.

The diagnosis of sensitiveness to smoke can be best made through history, observation by the patient, and testing by exposure to smoke as encountered naturally and to the solutions mentioned on page 120.

The most effective treatment lies in avoidance of cause.

### Dust

Normal individuals are affected to a certain extent by mechanical irritation of the membranes by dust. Many patients with nasal or bronchial reaction caused by sensitiveness to pollen and other substances, are made worse by the effect of dust. This is no doubt frequently due to the nonspecific irritating effect of dust. Certain individuals, however, are apparently affected chiefly or solely by dust; in fact, by dust of certain types. The fact that dust may be a specific factor in the etiology of bronchial and nasal reaction, was brought out in a very clever research by Cooke and his associates, who demonstrated that patients may be sensitive to the dust of certain houses and not to the dust of other houses, and that they may react locally or constitutionally upon the intracutaneous injection of dust extract.

Patients sometimes react specifically to one of several types of dust, such as stable dust, stock yards dust, house dust, or road dust. The constituent of dust which causes reaction can occasionally be identified with some known substance, such as animal hair or pollen, or substances used about the house, such as insect powder. When one has in mind the almost innumerable substances which may be contained in dust, one can readily understand that it should theoretically be a common and specific cause of nasal and bronchial reaction.

The simplest method of diagnosing reactions of this type, lies in the use of extracts of the suspected dust. This frequently gives rise to a local or general reaction upon intracutaneous injection. This is strong presumptive evidence that it is the source of illness.

Treatment depends upon the cause of the reaction. Avoidance of cause is best if this is practical. In the case of sensitiveness to a constituent which is widely distributed, specific treatment may be advisable.

### Food Idiosyncrasies

Food is an important source of allergy, but does not rank with pollen as a cause of bronchial or nasal reaction. It is, however, a

rather frequent cause of symptoms which occur as part of a general reaction, such as hives, angioneurotic edema, dizziness, hypotension, irritable bladder, etc.

Food may cause reaction in different individuals in different ways. In some, only through direct contact between a food and surface tissues of the gastrointestinal tract. In others, only after digestion and absorption. In the latter cases, reaction is apt to be delayed. Nasal reaction in food cases is frequently a result of contact between the nasal mucous membrane and volatile substances emanating from the foods during mastication.

Foods which sensitize may be protein or nonprotein, organic or inorganic. Some foods, such as sea foods, have a greater faculty for sensitizing than others, such as the commonly eaten meats, fruits, vegetables, or grains. This has been attributed by Eustis to the high content of the former in histamine-like bodies. The capacity of a food for sensitizing, however, is not necessarily the result of some peculiar chemical constituent. It seems frequently the result of mode of contact.

Patients are rarely sensitive to the bulkier constituents of the more commonly eaten foods, such as the proteins of beef. They are more frequently sensitive to foods which are rarely eaten, or to substances contained in traces in the commonly eaten foods. I have observed very few cases sensitive to beef, and these were all sensitive to cooked beef. They were not sensitive, therefore, to the bulkier protein constituents which are coagulated by heat. In one case, sensitiveness was traced to foods rich in purin basis. This included all meats, foul, fish, meat soups, gravy, tea, coffee, chocolate, and even peas and beans. Patients sensitive to milk are rarely sensitive to casein but rather to the constituents of milk contained in traces, such as lactalbumin fraction. In some cases, sensitiveness can be traced even to foods eaten by the cow which are secreted in the milk. Sensitiveness to honey is not uncommon, and in this instance, the source of the illness can usually be traced to the flower from which the honey was obtained. Doctor Gerald B. Webb and Dr. Ralph Matson each related to me the case of patients sensitive to egg, who could eat the meat of a rooster but who could not eat the meat of a hen unless the viscera were carefully removed immediately after it was killed. As previously mentioned one case sensitive to whole cooked egg reacted with asthma

upon the ingestion of traces of egg, but could tolerate rooster meat in almost any quantity. This patient, like the above cases, had asthma whenever she ate hen meat. In one food sensitive case, reaction was traced specifically to canned foods which invariably caused illness. The patient could tolerate any food in its natural state, or when cooked.

As previously mentioned, patients are not often sensitive to the grosser constituents of foods which they eat commonly. They are more frequently sensitive to the smaller constituents such as substances contained in the peeling of fruit or vegetable or in the husk of grains. It is important to bear this point in mind when making extracts for skin testing, and for treatment, for unless the whole article is used, the very substance responsible for illness may be lost.

The above facts may be explained possibly by an assumption that if patients should become sensitive to a bulky constituent of a common food, they should either lose their life or gain tolerance through frequent gross contact.

**Multiple Sensitization.**—Patients are occasionally sensitive to one food only. As a rule, however, they are sensitive to more than one. They may be sensitive to a group of somewhat similar foods, such as sea foods, or to several groups of foods which seem related, such as a group of fruits and vegetables. They frequently seem sensitive to a digestive or putrefactive product common to several foods. It seems probable through a comparison of sensitiveness of this type, with sensitiveness to air-carried substances, that multiple sensitization is due not so much to sensitiveness to many chemical bodies, but rather to sensitiveness to one specific chemical body which is common to many foods. Persons sensitive to foods are rather frequently sensitive to air-carried substances, such as dander or pollen.

**Specificity.**—Specificity in the case of food sensitiveness is apparently not so common or marked a feature as it is in the cause of sensitiveness to air-borne substances. However, it may be a marked feature in some cases. One egg sensitive patient could tolerate raw or boiled egg but not the egg contained in cake or cooked noodles. Multiple sensitiveness is common in food cases. Furthermore, delayed reactions are more common. These facts may be accounted for on an assumption that in the case of sensitiveness to foods, the patient may be sensitive to a specific chemical body

common to several foods which is liberated through the action of digestive juices, bacteria, or both.

**Sensitiveness and Tolerance.**- Sensitiveness to foods is much less permanent and much less constant than is sensitiveness to air-borne substances, such as pollen or dander. In the latter case, sensitiveness is usually permanent and rarely changes in degree. A person sensitive to pollen apparently always reacts if he comes in contact with a sufficient quantity of pollen. The same is apparently true in the case of sensitiveness to foods when reactions occur as a result of direct contact between a surface and the food, especially if the reaction is immediate. For example, the immediate reaction which follows the ingestion of honey is apparently as constant and permanent as pollen sensitiveness. It resembles very much in this respect the nasal reactions caused by pollen. Egg and milk sensitiveness, however, is variable, and is not necessarily permanent. This is especially true in the case of delayed reactions. One patient, for example, who was sensitive to milk and to almost any product of vegetable life, was violently ill for weeks, because of unavoidable contact with traces of these agents. She gave marked delayed skin tests. After a period of several weeks, she became tolerant of practically every substance to which she previously reacted and furthermore gave negative skin tests. She gave a history of having had attacks of hives, angioneurotic edema, abdominal pain and asthma for periods of several weeks at previous times during her life, and several months after I saw her she had an attack lasting several weeks. To account for variability in reaction to foods of this character, we might assume that the patient is sensitive to some chemical body liberated through physiologic processes, which are active at times and inactive at others. We know in the case of pancreatic juice, that its ferments vary according to the foods ingested. If an animal is fed on a fat-free diet, the pancreatic juice loses to a marked extent its fat-splitting ferment. This ferment is again elaborated if fat is added to the diet. It seems perfectly logical to assume in the case of sensitiveness to a split product of a food, that the capacity of that food for causing reaction would be dependent upon a great many factors, such as ferments, putrefactive bacteria, etc., and in the absence of these, its capacity for causing reaction might be lost. This assumption is not out of harmony with Vaughan's theory of protein split products and may be used to explain the marked

variability in reactivity against foods, especially in the case of delayed reaction.

The diagnosis of food sensitiveness is best made by history, observation by the patient, and by ingestion tests made with foods as eaten by the patient. Skin tests in food cases are often unsatisfactory. The truthfulness of these statements is exemplified by the egg sensitive patient just referred to who could tolerate a small amount of raw egg or boiled egg relatively well but who had asthma invariably if she ate the trace of egg contained in a very small piece of cake or noodles.

I may mention here also Meixner's patient (to be cited in detail subsequently) who had asthma after the ingestion of salted roasted peanuts but who could tolerate roasted peanuts if they were unsalted and salted peanuts if not roasted. The truthfulness of these statements should not be doubted if one considers the marked and varied changes which can occur in the structure of large molecules when heated under varying conditions of moisture, salt concentration, and hydrogen-ion concentration.

The simplest method of treatment lies in avoidance of cause except in the case of sensitiveness to foods used so commonly in cooking as egg, milk, and wheat. In this case, specific treatment is advisable. Specific treatment usually is most effective when given by mouth. The agent should be used therapeutically, prepared in the way in which it causes reaction. Otherwise, treatment may fail. Treatment with boiled and raw egg in the case above cited did not desensitize for cake or noodles.

### Drug Idiosyncrasies

Drug idiosyncrasies have been observed and discussed since the early days of medical science. Cooke and his associates have drawn attention to the similarity between their manifestations and those of reaction caused by pollen and similar agents. It is not uncommon to observe patients who are made ill by small doses of a drug and react with symptoms which have no resemblance whatever to the pharmacologic effect of the drug. Interesting in this respect are the alkaloids, including morphine, codeine, heroin, quinine, atropine, cocaine, novocaine, and apophysin; the coal tar products, especially aspirin, which is a relatively common cause of sensitiveness; the arsenic containing drugs, including arsphenamine and similar prep-

arations; and even the inorganic salts, including the iodides and bromides.

Many remedies, which have been called heart depressants, have gained this reputation for no reason other than that they tend to sensitize and cause reaction. Each of several patients who were made ill by aspirin, were specifically hypersensitive to it, and had symptoms resembling those of reaction caused by sensitiveness to other agents. The illness in each case was caused by a small dose. The average patient can tolerate large doses; in fact, a majority of patients can tolerate without ill effect as much as 240 grains in 24 hours.

Almost every laryngologist has observed collapse following the use of local antiseptics. This occurred in one of my cases after an injection by a dentist of a little novocaine for nerve block. Many cases of nervousness and apparent illness following local anesthetics, however, are caused by the pharmacologic action of epinephrin rather than by the anesthetic. The more severe illnesses, however, are usually the result of sensitiveness to the drug itself. I once referred a patient for tonsillectomy with the advice that a general anesthetic be used because of our finding of sensitiveness to cocaine. In spite of this, however, the laryngologist used local anesthesia and as a result spent the next hour, not in operating for which the patient was referred, but in trying to resuscitate the patient. It is interesting in this connection to mention drugs of the cocaine series as a relatively common cause of dermatitis in dentists; in fact, one of the most severe cases of the type which I have examined, was a dentist in whom the cause of his disorder was traced to the infinitesimal amount of novocaine with which he came in contact in his work with nerve block.

Worthy of especial mention is sensitiveness to arsenic because of its usefulness in the treatment of syphilis. The majority of cases which react to salvarsan are sensitive not to the drug itself, but to impurities contained in water which has not been properly prepared. However, occasionally patients react immediately after the use of arsenic preparations, even when the water has been prepared with perfect technic. In several cases of the type observed by the writer it was necessary to discontinue the use of both arsphenamine and neoarsphenamine on this account. Among patients who had the so-called "nitroid reaction," a family or personal history of

hay fever, asthma, or hives was obtained in as high a proportion of cases as in pollen sensitive cases.

Patients frequently are not sensitive to a drug, but to an impurity contained in the drug. This is very evident in patients made ill by salvarsan in which the sensitiveness can be traced to impurities in distilled water. One case even more striking than this was that of a patient sensitive to aspirin. He claimed he could take aspirin without ill effect. It was found almost by accident that he was sensitive to only one of five preparations of aspirin. A very small dose of one of the preparations invariably caused abdominal colic. The other four he could take with impunity.

A large number of cases were tested routinely during a period of one year with the following drugs: heroin, morphine, codeine, strychnine sulphate, quinine, cocaine, novocaine, atropine sulphate, hyoscine, caffeine, theobromine, digitalis, digaline, strophanthus, pilocarpine, phyastignine, and histamine. Almost every case gave a hive with pseudopods when tested intracutaneously with drugs of the morphine series (in 1 to 1000 solution)—that is, to morphine, codeine, and heroin. Very few gave positive tests with the others. Very few of the patients were clinically sensitive to morphine although a number stated that they reacted with symptoms such as nausea and vomiting after its use. One patient gave a history of reaction with typical symptoms of shock upon several occasions when morphine was given for gall bladder colic. This case gave a strong positive skin test to morphine but no stronger than several who were not clinically sensitive.

As previously mentioned, morphine, codeine, and heroin give positive skin tests (hives with pseudopods) in the great majority of normal people—in fact, give a stronger test than a solution of histamine in the same concentration. Histamine also consistently gives a positive reaction but rarely one with pseudopods. It would be interesting to know whether or not this capacity for producing hives bears any relationship to the remarkable habit producing capacity of drugs of the morphine series.

The diagnosis of drug idiosyncrasies can usually be made through a careful history and skin tests.

The treatment lies usually in avoidance of cause.

## Bacteria

Normal individuals occasionally have nasal reaction or asthmatic breathing under the influence of acute or chronic infection in the nose, nasal sinuses, and bronchial tubes. The symptoms may crudely simulate illness caused by pollen or other such agents. This is purely and simply the result of infection, however, since infection can cause marked swelling of the mucous membranes.

Patients with nasal or bronchial reaction due to any cause are usually made worse by infection although the reverse is the case in rare instances. Patients with egg asthma or pollen asthma may suffer severe exacerbations of reaction with the onset of an acute infection—in fact, both patient and physician may be misled and may be tempted to blame the entire illness upon the infection. Frequently patients with egg asthma give a history of relative freedom from symptoms except in the winter months when they have frequent attacks of influenza or bronchitis followed by prolonged asthma. Such patients upon an egg-free diet may continue to have influenza and bronchitis, but the attacks, under this condition, may last a few days only.

In patients who have asthma following colds, it is necessary to determine whether the infection is a primary or a contributory source of illness. Furthermore, it is necessary to determine whether the cold is an actual rhinitis or whether it is in reality an attack of nasal allergy due to reactions against pollen or some other non-bacterial substance. In several cases of fall pollen hay fever in which symptoms continued during the winter months, combined sensitiveness to pollen and cold were found (see Part II). The winter reactions caused by cold sensitiveness could easily have been mistaken for acute or chronic infection or for ''bacterial anaphylaxis'' or ''bacterial allergy'' which condition has seemed to me to be very rare and difficult of proof.

In addition to the irritating effect of infections which are in no wise related to hypersensitiveness, there are undoubted cases of reaction of hypersensitiveness which occur as a direct result of acute infection. Rather frequently patients with acute tonsillitis or acute rheumatic fever, and other acute illnesses display hives, angioneurotic edema, and erythema which are undoubtedly manifestations of hypersensitiveness analogous to egg urticaria. This would not seem necessarily a result of hypersensitiveness to products of

the organism itself. It might be a result of reaction to some agent generated in the body fluids under the influence of bacteria and even a reaction to heat (see Part II).

Walker, Cooke, Koessler, Zinsser, and others believe that reaction can occur as a result of hypersensitiveness to bacterial proteins and have succeeded in sensitizing animals to bacterial proteins. Walker considers the condition relatively common. Koessler and others think it is rare.

Reactions which can be conclusively blamed upon infections, especially chronic infection, in my experience have been rare. This should harmonize with a view previously expressed that constant intimate gross contact gives rise to tolerance. If this is true, patients subject to chronic infection should gain tolerance for bacterial products through almost constant relatively gross contact and should cease to react. Even in acute infections of slow onset, such as typhoid fever, the gradual increase in exposure to bacterial proteins should give rise to gradually increasing tolerance so that reaction, should it occur, should be limited in its duration. This view harmonizes, it seems to me, with facts as we know them now. In few instances I have obtained frank positive skin tests with bacterial proteins but as a rule they give either negative tests, indefinite tests, or delayed reactions. The delayed inflammatory reaction occurring twenty-four hours after the injection of Staphylococcus aureus or B. coli is almost a constant finding but differs markedly from the hive reactions obtained with pollen and hair.

The diagnosis of reaction of bacterial allergy is difficult. The history may be very misleading and unless frank positive skin tests with pseudopods are obtained, there is little but negative evidence upon which one can base a diagnosis. Diagnosis based on negative evidence retards progress and misleads.

The treatment depends upon removal of cause if possible and symptomatic remedies.

### Insects and Animal Parasites

The sting of certain insects causes local itching and pain or an inflammatory reaction or even a wheal at the site of the sting in the majority of individuals. The sting of certain insects, such as the spider, is likely to be quite poisonous to the average individual. A small proportion of persons become specifically hypersensitive to

the sting of certain insects and react to them with general symptoms of greater or lesser gravity. Occasionally the symptoms are very grave indeed and in one case cited to me by Dr. J. R. Newman, Fort Scott, Kansas, death quickly followed the sting of a wasp.

A number of years ago, a physician practicing medicine in a small country town related to me the case of a patient whom he had seen in a state of complete collapse who was asthmatic and almost pulseless and who showed, on examination, a huge area of angioneurotic edema around a small lesion which he thought was an insect bite. He quickly administered adrenalin in large doses with speedy recovery of the patient. A case very similar to this was reported by Dr. Canby Robinson in 1921. A patient observed recently had not only hives and generalized erythema after being bitten by mosquitoes, but nausea, vomiting, abdominal pain, and diarrhea. A history of similar reactions of lesser severity has been obtained from patients who reacted to the bites of chiggers, fleas, hornets, or bees. In one case of subacute urticaria, the patient was found to have scabies and following treatment for this condition, the hives disappeared.

One wonders to what extent the eosinophilia in diseases caused by animal parasites, such as hydatids, trychinae, filaria, and amebae can be traced to reactions of this kind caused by sensitiveness of the patient to materials liberated by the parasites. The rarity of outspoken hive reactions in cases of this kind might be attributed to tolerance gained through the intimate constant contact.

The diagnosis of reaction occurring as a result of an insect bite can be obtained in the average case from history and examination.

The treatment in shock cases should be symptomatic with atropine and adrenalin. In addition to this, the patient should be cautioned about the danger of insect bites. In a highly sensitive individual, the sting of a certain insect might cause a more violent illness than the bite of a poisonous reptile.

CASE 2.—*Death Following the Sting of a Wasp.*—The patient, a girl of six, gave a positive family history for allergy. While playing in her yard at her mother's side, in apparent health, she suddenly screamed. The mother turned quickly to find her pale and gasping for breath. She noticed a wasp on the child's arm and knocked it off, picked the child up, and ran for her door. Before she could lay the child down, which was within less than one minute, she had apparently breathed her last.

This case, observed in 1920, was diagnosed by Dr. J. R. Newman, as death

caused by anaphylaxis due to the sting of a wasp. He thought the only chance of error in diagnosis lay in the fact that some violent poison may have been inoculated intravenously by the sting.

## Therapeutic Sera

The danger of illness, or even sudden death after the use of therapeutic sera, is now well recognized. The illness may be of two varieties, either the immediate, sudden, stormy illness, resembling shock, or an illness characterized by fever, hives, angioneurotic edema and joint pains, described under the term "serum sickness" by von Pirquet and Schick. The latter occurs characteristically from eight to thirteen days after the injection of serum. The former illness recognized by Rosenau and Anderson, was thought to be a typical manifestation of anaphylactic shock caused by a second dose of foreign protein. Serum sickness occurs more quickly and is more severe after second doses of serum but shock occurs more frequently after a first injection than after a second. According to Coca, it occurs usually in patients with naturally acquired hypersensitiveness to horse serum. Naturally acquired sensitiveness to horse serum may be surprisingly intense—in fact, Boughton reports a case of death following the intravenous injection of one drop of horse serum. Several fatal issues have been reported following the subcutaneous injection of one c.c. of horse serum, and many following the injection of therapeutic doses of diphtheria antitoxin. There are, therefore, apparently two factors concerned in reaction to foreign sera, first, the one caused by naturally acquired hypersensitiveness to the serum, which may give rise to reaction following a first dose, and secondly, the one (serum sickness) which commonly follows large doses of serum, in nonallergic individuals especially when it is given intravenously. This reaction is intensified by a first injection and may cause a patient to react with unusual severity after a second dose. The fact that second doses are less to be feared than first doses has been emphasized by Coca, who states that if a patient tolerates one dose, he can almost certainly tolerate a second.

Patients who are naturally sensitive to horse dander are not necessarily sensitive to horse serum. This fact harmonizes with the experience of Wells and others, who show that animals sensitized to the proteins of certain seeds, are much more sensitive to the

homologous proteins of seeds of a different species than to different proteins derived from seeds of the same plant. This is true of proteins of animal origin and not only of animal sensitiveness, but of human beings with natural hypersensitiveness as well. This is exemplified by the following case.

CASE 3.—*A Patient Sensitive to Horse Dander Who Tolerated Horse Serum.*— The patient, a physician of forty-five, consulted me because of asthma. I did not have the opportunity of examining him completely, but obtained the following data which pertains to the subject:

The patient complained of being sensitive to "everything," including horses. He had been unable for years to ride in a carriage or buggy because of attacks of asthma. Upon questioning it was found that in the past he had taken three doses of horse serum subcutaneously and had withstood each practically without visible ill effect.

Upon being tested cutaneously with horse dander, he gave a marked reaction. Upon testing cutaneously and intracutaneously with horse serum, he gave a negative reaction.

If physicians are acquainted with the dangers attending the use of therapeutic sera in sensitive patients, the danger in its administration is actually reduced to almost nothing. Fortunately, children stand sera and foreign agents of any sort better than adults. It is probably for this reason that death following the promiscuous use of sera in human beings is so small. As age advances, the chance of reaction is greater. For this reason, it is especially in adults that inquiry as to the possibility of natural sensitiveness to serum should be made before serum is administered. This, as a rule, can be accomplished without great effort. One should inquire concerning a family and past history of hay fever, asthma, hives, and eczema. If a positive history is given in either case, the patient should be tested intracutaneously with $\frac{1}{100}$ c.c. of horse serum. Even in the case of a negative result, the dose of serum administered should be reduced to the smallest amount compatible with a good therapeutic result. This is actually much smaller than the dose ordinarily advised in the treatment of diphtheria. In children, from one to three thousand units will almost always suffice to cure the patient. After the administration of serum, the patient should be watched, and in case of reaction, atropine and adrenalin should be used freely. If a positive intracutaneous test with horse serum is obtained, serum should not be administered unless the indication for its use is sufficient to warrant the dangers coincident

with reaction. In this case, it should be administered according to Coca's method described previously, and medicants for the treatment of reaction should be close at hand ready for immediate use.

## Shock as Result of Blood Transfusion

Before the discovery of iso-agglutinins, the dangers of blood transfusion were great. In fact, while a medical student and interne I observed three cases of death during, or a few hours after, a transfusion of blood. Inasmuch as transfusion was rarely performed at that time, these three cases represented a very high mortality ratio and were due, no doubt, to the use of incompatible donors. Since the method introduced by Moss and Brem for the grouping of donors according to their iso-agglutinins has been broadly used, reactions from blood transfusion have become much less common, and with the use of criteria as outlined by Lindemann in the performance of blood transfusion severe reactions are rare.

The following case is reported as one of two examples of severe reaction which occurred during blood transfusion, in individuals whose blood had been tested with faultless technic so far as iso-agglutinins were concerned. Inasmuch as the reactions occurred immediately after the introduction of the first syringe of blood, the reaction could hardly be blamed upon anything except some incompatibility in the donor's blood which had not been discovered. This was thought to be hypersensitiveness on the part of the patient to a food which had been eaten by the donor, and is analogous, I believe, to the reactions often observed in infants, due to hypersensitiveness of the infant to some article of food eaten by the mother which is secreted in the milk.

CASE 4.—*Shock as a Result of Blood Transfusion.*—The patient, a woman of sixty-three, had an outspoken case of pernicious anemia. Pallor had been noticed by the patient for several months. She had, in addition to the anemia, a slight grade of hypertension and slight cardiac hypertrophy. She gave a history of having been subject to asthma at odd times in her life, and that she was unable to tolerate milk.

She was given a transfusion by the Lindemann method of 1000 c.c. of blood taken from a very large donor. At the end of this transfusion, she was still moderately anemic. No ill effect was noticed. Fifteen minutes later, when the second donor was brought in, she was talking brightly, had normal pulse, and apparently felt improved. The second donor was prepared and she was given 20 c.c. of blood. Before the second syringe of blood could be injected, she said she felt a pain in her back, and within a moment she became uncon-

scious—in fact, deeply comatose. Her pulse vanished, she stopped breathing, turned blue, and I thought she was dead. She was given three injections of adrenalin solution 1:1000 subcutaneously in 1 c.c. doses, and in about five minutes she began to breathe, move, her pulse returned, and within fifteen minutes she was again relatively normal. She has had no illness or untoward symptoms since this time, and her blood count has gradually increased, under the influence of the one transfusion which was given, to 4,000,000.

Since the patient's serum with donor's corpuscles showed no agglutination upon testing, I felt sure that the reaction described could not have been caused by iso-agglutinins. There seemed to be only one other reasonable explanation of the reaction, namely, hypersensitiveness on the part of the patient to milk. The patient was tested intracutaneously with all the common foods and gave a striking positive reaction to milk. Each donor likewise was tested out to all the common foods, but gave negative tests to all of them. We felt, therefore, that the reaction was in all probability due to sensitiveness on the part of the patient to some constituent of the donor's blood—probably a digestive product of milk. Milk had been taken in considerable quantity by the second donor previous to the transfusion.

Hives have been observed to appear during or soon after transfusion of blood on numerous occasions. Symptoms resembling anaphylactic shock are by no means unknown, and have been attributed to agglutinins, hemolysins, etc. I have observed one other instance of reaction resembling shock in a patient who was proved sensitive to tomato and cabbage and for whom a donor had been used who had recently eaten tomato and cabbage. The bloods of patient and donor were thoroughly compatible so far as iso-agglutinins were concerned, and I could discover no other adequate cause for the reaction.

The testing of blood for compatibility is, I believe, not the whole story in the choice of donors for blood transfusion and, in spite of the greatest care reactions, will occasionally occur, even reactions of the greatest possible severity, due to hypersensitiveness on the part of the patient to some constituent of the donor's blood.

For this reason, I have changed my technic in the performance of blood transfusion and now make a preliminary inquiry for a family and personal history of hay fever, asthma, and hives before a transfusion is started. Furthermore, I always inject a small amount of the donor's blood (5 c.c.) intravenously before beginning

the transfusion. If this produces no reaction after an interval of several minutes, the blood is considered probably compatible and the transfusion is started. In patients giving a personal or family history of hay fever, asthma, or hives, transfusion is avoided unless urgent enough to justify the danger of a severe reaction. In this case, a preparatory hypodermic of adrenalin is given.

This precaution, I believe, reduces to almost nothing, the few chances of mishap in the direct transfusion of blood.

### Sensitiveness of One Individual to Another

One frequently wonders whether one individual can become sensitive to another. I have been questioned concerning this possibility by many physicians. Dr. W. C. Manchester of Alliance, Ohio, once related to me the case of a child who had spells of asthma whenever the mother menstruated. It was free of attacks at other times and free of attacks if kept away from the mother during the menstrual period. I once observed the case of a patient who had attacks of asthma whenever he was closely associated with a certain girl. I did not have an opportunity of determining the exact source of the attack, but presumed he was sensitive to an article of clothing, perfume, rather than to the individual herself.

The fact that it is impossible for one individual to be sensitive to another seems perfectly evident from the two cases alluded to previously in which shock occurred as a result of blood transfusion. Here there can be no possible doubt that the patients were excessively sensitive to the blood of the donors and reacted with typical symptoms of shock. As mentioned, the blood of patients and donors was compatible so far as agglutinins were concerned. If individuals can be sensitive to the blood of other individuals, it seems quite likely that they could be sensitive to other body fluids, or secretions and might react upon intimate contact. This type of sensitiveness, no doubt, exists but must be quite rare. It would seem of practical moment, chiefly in the case of a need for blood transfusion.

### Endogenous Allergy

One frequently wonders whether or not certain individuals become sensitive to substances originating in the body proper. Substances absorbed from the alimentary tract are in reality exogenous in origin since the alimentary tract is nothing more than a tube

passing through the body, and substances contained in it are outside the body in the same sense that substances are outside the body proper when in contact with the mucous membrane of the mouth or the skin. One would not believe it likely that individuals could become sensitive to and react to substances of endogenous origin which are present constantly in bulk. Such substances of this nature should either cause death or give rise to tolerance so that in the course of time patients should cease reacting to them. However, conditions frequently arise which make one suspect sensitiveness to a body substance which is produced or distributed only under unusual circumstances. This view, however, is difficult to prove. In one case observed by the writer, severe manifestations of allergy appeared each month just prior to menstruation. The attacks were associated with dysmenorrhea, and ceased immediately when the flow from the uterus was established. In three cases patients suffered a severe attack of allergy coincident with the weaning of a baby. The attacks could be relieved by the free use of a breast pump. In one case observed by my assistant, Dr. Stofer, the patient gave a definite wheal upon intracutaneous injection of her own milk and gave negative skin tests to every other substance with which she was injected. She even gave negative skin tests to cows' milk.

The following case reported is interesting in that in symptomatology it resembled serum sickness.

CASE 5.—*Hives and Angioneurotic Edema Following the Weaning of a Baby.* —The patient, a woman of twenty-nine, gave the history that her mother had suffered from hives for a number of years. She herself gave a negative history of hay fever, asthma, or hives, but said she reacted markedly on several occasions to the sting of bees. After the birth of her first child she was normal in every way and nursed the baby for a period of nine months. The baby was then fed on a bottle prior to each nursing during a period of about ten days. The bottle was then substituted for breast feedings until finally the number of nursings were reduced to two each day. Breast feedings were then discontinued altogether. About twelve hours after the last feeding the breast caked, became swollen and very painful. The patient began to itch from head to foot. Hives appeared over the skin generally. The lips began to swell and the patient became very dizzy. She was given atropine and adrenalin in large doses, and the symptoms subsided quickly. She was kept under this medication for several days until the secretion of breast milk nearly ceased. Since then she has had no recurrence of her trouble. Several months after this the patient was tested intracutaneously with about 200 different substances with negative results.

It cannot be inferred from the above case reports that endogenous allergy exists, although this would offer a simple explanation of the phenomena observed. Retention of uterine secretion in the one case and retention of breast milk in the other cases may simply have been contributing factors overthrowing a balance which allowed the patient to react to some other foreign agent.

Additional evidence in support of the view that endogenous allergy might exist will be presented under the term "physical allergy" in which patients react solely and specifically to the action of physical agents. If reaction to physical agents (similar as it is in symptomatology to the subject under discussion) proves to be the same in pathogenesis as pollen disease, it seems easily possible that patients under certain conditions can become specifically sensitive to some new substance produced solely and specifically under the influence of a physical agent, such as light, heat, cold, mechanical irritation, freezing and burns.

# CHAPTER XII

## CONTRIBUTORY CAUSES OF REACTION

In the previous chapters have been mentioned a number of the more common agents which sensitize and cause reaction. Patients who are reacting or who are on the verge of reaction, are frequently made better or worse by factors to be described in this chapter—factors such as chemical irritation, mechanical irritation, the irritation caused by heat and cold. They may be influenced for better or for worse also by reflexes, by functional activity, by conditions which influence a person's state of general health, such as by disorder in the glands of internal secretion, by pregnancy and menstruation, and by diseases such as infections, or functional or organic diseases which may coexist. I do not wish to say in this chapter, as I have in earlier communications, that the effect of these so-called contributory or secondary factors can always be substantially proved. In fact, since then I have been forced by evidence obtained through a study of reactions caused by heat, cold, mechanical irritation, and light to change my views completely. I have been unable, in the majority of cases studied recently to bring out reactions such as hay fever or hives through the application of physical agents, such as light, heat, cold, or mechanical irritation except when the patients are sensitive specifically to the agent used which caused reaction. At the present time, I am convinced that many of the so-called contributory causes of reaction are actually primary causes and seem deceptive because they frequently exert their influence more intensely when combined with the action of another agent to which the patient reacts simultaneously. For this reason, a fundamentally primary cause may appear to be a contributary or secondary cause.

Contributory factors, if such exist, apparently may either precipitate an attack or may relieve an attack. For example, a patient with pollen asthma often reacts to smoke of some variety during the pollen season and tolerates it relatively well at other times. Opposite to this may be mentioned a patient who was subject to severe attacks of nasal reaction who could invariably and immedi-

ately relieve himself by inhaling tobacco smoke. While I do not, at the present time, wish to endeavor to account for some of these remarkable facts except as above outlined, I, with equal certainty, do not wish to deceive myself or the reader by calling such reactions simple reflexes and consider the matter demonstrated.

In the following paragraphs will be described a number of factors which appear frequently to be contributory or secondary causes of reaction. Further study may prove that they are more often primary than secondary—in fact, it may turn out that they are almost always primary.

### Mechanical Factors

Patients who are reacting mildly or who are on the verge of reaction caused by pollen or other material agents, are often made worse by mechanical irritants. For example, asthma is often made worse by the inhalation of dust. It is also made worse by dyspnea caused by overexercise and is frequently made worse by coughing or laughing. The effect of these agents is so marked in certain cases that a slight cough often precipitates violent attacks. In some patients who appear to be reacting mildly with dermatitis or wheals, the reaction may be made severe by rubbing the skin or scratching the skin. Patients having alimentary reaction often have severe dyspeptic symptoms after the ingestion of rough foods, such as nuts or the peeling of fruits or other foods which can irritate mechanically.

Whereas the above facts characterize many cases, there are an equal or greater number of cases having classical urticaria, classical asthma, and classical alimentary reaction which are absolutely unaffected by mechanical irritants of any sort. Furthermore, there are many cases in which the skin reacts to the slightest mechanical irritation, such as scratching or rubbing, which are absolutely unaffected by the action of any other agent, either material or physical, which can be applied to the skin. In many cases of this type, I have tried the action of intracutaneous injections, chemical irritants, even chloroform liniment applied to the skin until it caused severe burning, ice rubs, heat applied almost to the point of producing a burn, all without the slightest influence whatever in the direction of producing either abnormal erythema, itching, or a hive. In cases of this variety, mechanical irritation is usually a primary cause of reaction (see Part II).

## Chemical Irritants

Many patients with nasal reaction or bronchial asthma due to pollen or other material substance, are apparently made worse by the nonspecific irritating effect of certain vapors, such as formulin, turpentine, ammonia, sulphur dioxide, irritating coal or wood smoke, the smoke from a gasoline motor, and even by perfumes.

Patients reacting mildly or on the verge of reaction with symptoms such as eczema or urticaria, frequently react more severely under the influence of certain chemicals applied locally, such as chloroform, irritating ointments, or lotions, and even under the influence of mild acids or alkalies, such as extremely dilute acetic acid or soap. Patients with alimentary reaction are frequently made worse by the effect of chemical agents upon the mucous membrane of the stomach, such agents, for example, as mustard, pepper, alcohol, and acids. Such cases may react even to agents which stimulate the secretion of gastric juice, such as salt or sugar.

It is extremely difficult in the majority of cases of the above types to say that the action of the chemical bodies is strictly secondary and that reaction is not a result of actual combined sensitiveness.

## Light

A few patients with dermatitis are definitely made worse by the effect of light—in fact, by light of certain specific wave length. This influence, however, has seemed, in my experience, primary in every case—that is, in the patients who reacted to light, reaction could be brought out so consistently at all times under the influence of light and by light alone that it was looked upon as being the primary factor.

## Cold

In many patients with nasal reaction or bronchial asthma, a severe attack can be precipitated by the effect of cold locally upon the membranes of nose and bronchial tubes or by the effect of cold upon the skin, or both.

Patients with dermatitis or urticaria are frequently made worse by the local effect of cold. In one case of pollen allergy, attacks of severe abdominal pain could be brought on by the ingestion of cold water or cold food.

In the majority of cases where the action of cold has been studied carefully, it has been found that the patient is actually specifically sensitive to the action of cold and I really believe that patients having reactions which are markedly influenced by this agent are specifically hypersensitive to it. In other words, cold is more frequently a primary cause than a contributory of reaction and patients having asthma due to causes other than cold who react specifically to its effect are usually cases of combined sensitiveness (see Part II).

### Heat

Many patients having nasal reaction or bronchial asthma due to causes other than heat are made worse by the effect of heat either locally upon the membranes or by the effect of heat upon the skin or of heat generated by exercise or by any combination of these. The same is true of patients who react with dermatitis or urticarial lesions. In one patient with alimentary allergy of unknown origin, a severe attack of diarrhea would invariably follow the ingestion of hot drinks or hot foods.

Whereas it is possible in many cases such as these that the effect of heat is secondary, certainly in a larger proportion the effect is primary—that is, the patient reacts primarily and specifically to the effect of heat. (See Part II.)

### Functional Activity

Many patients who are subject to reaction are apparently made worse by functional activity. I think this is the rule rather than the exception. It will be proved in Part II that reaction made worse by functional activity is often actually caused by the heat produced thereby. However, in addition to this, functional activity apparently affects reaction caused by other agents. For example, in patients with pollen asthma, symptoms were apparently made worse by the dyspnea caused by exercise or disease. Opposite to this, it must be mentioned that in cold sensitive cases asthma may be completely relieved by severe exercise, even when the primary effect is dyspnea. Patients reacting with dermatitis or urticaria are occasionally made worse by sweating. Patients reacting with stomach symptoms are often made worse by the effect of a heavy meal.

### Reflexes and Emotional Disturbances

Reflexes frequently have a marked effect on the symptomatology of reaction, either in making it worse or better. In discussing this, I realize that I am treading upon uncertain ground. Frequently, by a reflex, the patient may be simultaneously exposed to the action of an agent to which he is sensitive and reacts. It is well known that some asthmatic cases are made better by the effect of an emetic, by defecation, by eating, and even by exercises, mental excitement, and emotional disturbances, while others are made worse. In many such cases, I have been able to satisfy myself that the change in symptoms was not actually the result of a reflex, but was actually a result of exposure to the effect of heat or cold. For example, a number of cases who are made worse by physical exercise, excitement, and emotional disturbances, such as crying and laughing, were heat sensitive cases. Similar reactions could be produced primarily by heat and could be prevented by cold. In other cases in which relief could be obtained by precisely the same agent, the patients were proved sensitive to cold and the relief which followed either physical or mental excitement, was due primarily and solely to the heat produced thereby. (See Part II.)

### Pregnancy and Menstruation

Many patients who are subject to chronic reaction are relieved completely during pregnancy. Others are made worse. The same can be said concerning menstruation. In this case, one would be inclined to believe that the effect is usually secondary and often a result of a disturbed balance in the activity of the organs of internal secretion. In some cases the effect can be traced, I believe, to caloric sensitiveness, and the changes in body temperature and heat production caused by the unusual condition.

### Endocrine Glands

The organs of internal secretion evidently play a marked rôle in the symptomatology of reactions of hypersensitiveness. This should seem self-evident when we bear in mind that the great majority of cases, regardless of their severity, can be completely relieved through the action of adrenalin. Many cases can be relieved by pituitary extract. If adrenalin has a normal physiologic antagonist,

and one might easily believe that this is the case, an overproduction in this might, on theoretical grounds, give rise to a reaction. Thyroid extract in occasional cases is beneficial, especially in patients whose metabolism is below par and whose temperature runs markedly subnormal. The above influences from a practical viewpoint, are effective in many cases, but would seem usually to be secondary factors in the etiology of reaction.

### Nasal Defects

Nasal defects have more than an ordinary bearing in the pathogenesis of reaction. Rhinologists of some note have gone so far as to claim a high percentage of cures in cases of chronic asthma through radical operative work in the nose. Among one hundred pollen cases examined, a deviated nasal septum was found in 32 per cent of cases. Chronic nasal sinus infection was demonstrated clinically and by x-ray in only 6 per cent of seasonal cases and nasal polyps were found in only 10 per cent. Among one hundred perennial cases examined, 33 per cent showed a deviated nasal septum, 24 per cent had nasal polyps, and 27 per cent had unmistakable evidence of chronic nasal infection. Twenty-one per cent gave history of marked "predisposition to colds." These findings were quite different from those obtained in a similar examination of 100 bank employees, in which the nose and throat was examined as a routine measure. In these definite evidence of sinus infection was found in only 6 per cent of cases. The fact is that sinus infection in perennial cases seems a sequel of chronic reaction rather than a cause of reaction. With deviated septum found in about the same proportion as in the average individual, the superimposed chronic edema of the membranes caused by reaction would predispose mechanically to infection and to polyps. If once this condition is established, however, I feel sure that it can play a contributory rôle in the pathogenesis of reaction in the nose and bronchial tubes although I believe the influence is a minor one. The existence of polyps surely must change surface temperature in nasal mucous membrane and, as will be shown in Part II, the temperature of some structure in the nose has an important bearing upon the pathogenesis of nasal reaction—in fact, by heating and cooling the nose by hot or cold compresses, certain cases of nasal reactions can be controlled at will. In one patient subject to chronic perennial asthma in whom

a number of polyps were found upon examination, an attack of asthma could be precipitated by exerting a little pressure in the antrum during the process of irrigation by a rhinologist. It is by no means certain, however, that this effect was not the result of temperature change rather than pressure change.

This subject is important for many asthma cases and many patients with nasal reaction have been made infinitely worse by radical and even by minor operations in the nose, even operations carried out intelligently by the most careful surgeons. One patient, for example, has been a chronic invalid because of asthma since the date of a submucous resection made while he was serving in the army. Whereas, it is frankly admitted that careful nasal work occasionally gives marked relief in nasal and bronchial cases, as a rule the reverse is the case. Many chronic sufferers give a history of five to ten intranasal operations for polyps and upon examination, show that the nasal cavities are practically occluded with polyps. There are few instances in medicine where careful thoughtful work in surgery can do as little good or as much harm. Because of the latter, operative work should be done only as a last resort.

### Disease in the Alimentary Tract

It will be mentioned subsequently that patients subject to alimentary reaction show, in about 50 per cent of cases, a definite organic lesion in the gastrointestinal tract or its appendages. Occasionally surgical relief of these conditions and medical treatment of these conditions relieve the symptoms complained of. It is by no means beyond the realm of theory that organic disease in the alimentary tract can play a part in the pathogenesis of reaction. The intestine contains among other things a substance, histamine, which could produce reaction in normal individuals if absorbed.

# CHAPTER XIII

## GENERAL CHARACTERISTICS OF REACTION

Manifestations of reaction vary from symptoms so slight, as itching of the eyes, to symptoms so severe, as collapse and death, which may occur within a matter of seconds or minutes. In no clinical condition are symptoms more varied in nature, degree or severity, or in locality. Few tissues and few organs enjoy complete freedom from its effects.

Gross variation in the manifestations of reaction seems a result of differences in locality of reaction, in degree of reaction, and in chronicity of reaction rather than a result of any fundamental difference in cause and pathogenesis, for in almost every instance the primary effect seems fundamentally the same, namely, stimulation or inhibition of the activity of tissues as effected by stimulation of the autonomic nerve mechanism.

### Recognition of Symptoms of Reaction

Our knowledge of illnesses attributable to allergy is, at the present time, incomplete. As new symptom complexes are discovered and added, our understanding of the subject will advance and its clinical usefulness will become greater. Tempting as it is to add to our list of known symptoms some of the clinical conditions which now seem strange and obscure in origin, certain it is that the acceptance of any, unless substantially proved will detract from rather than promote interest in the subject and will reduce its clinical usefulness. Before a new symptom complex, therefore, is accepted as a definitely proved manifestation of allergy, it seems proper that at least four requisites be fulfilled if possible.

*First.*—That the agent directly responsible for the symptom be discovered.

*Second.*—That relief of the symptom be effected through removal of contact with the suspected agent.

*Third.*—That the symptom be reproduced during a well period by bringing the patient again into contact with the suspected agent in a more or less natural way.

It is inadequate to reproduce the symptom by hypodermic injection of foreign material since augmentation in allergic symptoms can arise through the nonspecific action of agents of this sort.

***Fourth.***—That it finally be proved beyond reasonable doubt that the symptom is actually allergic in nature.

The fourth requisite seems simple but actually presents difficulties. Finding that a suspected symptom is associated with other recognized manifestations of allergy, such as coryza, asthma, hives, eosinophilia, or that it occurs in individuals who give a personal or family history of such conditions, is presumptive evidence but not proof. As an illustration of a case in which this type of reasoning can lead to error may be mentioned a patient who had tabes dorsalis and who was specifically hypersensitive to apple and peach skin, and in whom lightning pains could be brought on at will by the eating of apples and peaches. It would be manifestly erroneous to assume from this that lightning pains can occur as direct result of allergy. In this instance, the error is easy to avoid because of the fact that the symptom "lightning pains" is so easily recognized as belonging to an illness other than allergy. In the case of a symptom such as headache, precordial pain, or convulsions, the causes of which are multiple, the chance of error is greater.

It goes without saying that the above requisites cannot be fulfilled in every instance and also that even if they are, the case is not positively proved. In many instances, only the weight of a great deal of data justifies a conclusion. However, working and reasoning along the above lines is relatively safe in the average case if one realizes the fallibility of his conclusions. As data accumulates, the true symptomatology of the condition will crystallize.

## Types of Reaction

When a patient is hypersensitive to a foreign agent, illness may be caused in the several important ways which follow.

1. **Contact or Local Reactions.**—These are characterized by reaction at point of contact between surface tissues and an agent to which they are specifically hypersensitive. For the sake of clearness, this will be spoken of as a *contact* reaction.

Examples of contact reactions are pollen hay fever, wool dermatitis, abdominal pain caused immediately by foods, and wheals at the point of application of materials used for skin testing.

Slight general reaction, such as eosinophilia and hypotension frequently accompanies contact reactions, especially when the surface area involved is large. Severe general reaction, such as erythema, itching, angioneurotic edema, and collapse is rare in contact cases. They do actually occur, however, when the patient is excessively sensitive, when the dose encountered is great, or when the surface area exposed is great. A patient referred to previously was so sensitive to animal hair that after walking by a zoo upon one occasion she not only had asthma and coryza but generalized itching, edema of the face, profound weakness, and collapse which was alarming.

2. **General or Constitutional Reactions.**—Constitutional reactions are characterized by disorder in distant organs occurring as part of a general reaction after the offending agent has been absorbed and distributed by the blood.

As examples of this may be mentioned asthma and urticaria caused by the ingestion of egg, abdominal pain and diarrhea following an insect bite, and reaction following the injection of therapeutic sera, pollen extract, or salvarsan.

3. **Solitary Reactions.**—Under this heading is designated reactions which are prone to occur over certain limited areas under the influence of a given stimulus. Reactions of the sort tend to occur always in the same locality and each time present the same general appearance. If the stimulus is unusually great, however, a widespread reaction may occur, submerging the solitary reaction.

CASE 6.—*Examples of Solitary Reactions.*—As an example of solitary reaction may be mentioned the case of a patient who was under treatment for specific disease. Upon the administration of salvarsan intravenously, there would appear invariably a few moments after the beginning of the injection a hive near the insertion of the deltoid muscle of the left arm. The hive always had the same locality, shape, and general appearance. The patient never had hives in any other locality at any time.

Another example of solitary reaction was observed in a patient who was sensitive to sunlight. Following exposure of the right elbow to light (15 seconds of summer sunlight) there would appear several hives which would invariably have the same location, shape, size, and general appearance. After more prolonged exposure of the same area to light (three minutes) a large hive would appear which would cover the entire skin area exposed.

A reaction of a similar nature made its appearance in another patient in the form of several hives on the chest which would appear whenever she was exposed to heat or took an undue amount of physical exercise or upon being markedly

wrought up mentally. The hives, like the previous ones, always occupied the same site on the skin and always presented the same general appearance.

Solitary reactions might be explained, possibly, by assuming that certain tissue elements hypertrophy through the effect of frequent reaction caused by frequent exposure so that further slight exposures might thereafter produce an unusually marked effect.

Huber and Koessler demonstrated marked hypertrophy of the muscles of the bronchial tree in patients subject to asthma. Similar hypertrophy might easily occur in areas other than the bronchial tree after frequent prolonged reaction and thus give rise to intensified reactions at those particular points.

Solitary reactions of the skin are of little practical import. I believe, however, that solitary reactions of a similar nature occur in other localities and in such, might be of great practical importance. For example, a solitary reaction in the bronchial structure might cause a high grade of obstruction and give rise to great respiratory difficulty in a short time and might manifest itself after very slight exposure to the agent which caused reaction.

4. **Nonspecific Reactions.**—When an organ is in irritable state as a result of reaction, it may be unduly disturbed by agents which ordinarily have little effect upon normal patients. A marked distinction must be made between this type of reaction and the reactions to be described under the topic "physical allergy" which apparently are caused solely and specifically by the action of physical agents—in fact, "nonspecific reactions" as here described are in all probability frequently examples of multiple sensitiveness—that is, the patients may not only be sensitive to the action of a material agent, but also independently sensitive to the action of a physical agent and that the two combined produce more reaction than either one alone.

It is not uncommon for an egg asthma case to be made worse by exercise, change in temperature, exposure to dust, or by an attack of influenza. This fact is frequently very misleading both to patient and physician, so that frequently a symptom due primarily to egg sensitiveness is blamed upon the physical case.

5. **Allergy as a Contributory Cause of Illness Due to Other Agents.**—Illnesses in no wise related to allergy are occasionally made worse by reaction. This is a common occurrence and is well exemplified by the patient previously referred to with tabes dor-

salis who is specifically hypersensitive to apples and peaches and who can bring on lightning pains at will by the ingestion of apples or peaches.

6. **Sequelae of Chronic Reaction.**—Illnesses frequently occur as a sequel of reaction, especially of chronic reaction. As examples may be mentioned nasal polyps which I am sure frequently result from chronic edema of the nasal mucous membrane caused by chronic reaction. Furthermore, in patients with chronic asthma, the mucous membrane of the bronchial tubes is swollen and presents an unusually good ground for the development of local infection in the tubes so that in patients of this sort, chronic bronchitis, or bronchopneumonia is not uncommon. Furthermore, may be mentioned such conditions as emphysema and even spontaneous pneumothorax which occurs occasionally in severe cases. Even symptoms resembling those of intestinal obstruction have been observed in the case of severe alimentary reaction.

### Differences Between Contact and General Reactions

Diagnosis is often simplified if a symptom can be classified as contact or general. This knowledge may be useful in therapy even when it is not possible to discover the agent primarily responsible. For example, in a case of allergic dermatitis, if it can be shown that the reaction is the result of contact with an air-borne substance, the vast number of agents, such as foods, which are commonly responsible for general reactions can be eliminated and the symptom can often be relieved by the use of a suitable covering for the skin.

Contact cases differ as a rule from general cases (Table III).

Surface reactions, such as coryza, asthma, abdominal pain, and dermatitis, can occur both as a result of surface contact with an offending agent or as a part of a general reaction. Some of the general symptoms, however, such as the neurologic symptoms, joint symptoms, hypotension, eosinophilia, hives, angioneurotic edema, etc., occur under ordinary conditions only as part of a general reaction after the agent has been absorbed and distributed by the blood. The presence of one or more of these latter symptoms, therefore, can almost always be looked upon as evidence of general reaction.

TABLE III

| | CONTACT REACTIONS | GENERAL REACTIONS |
|---|---|---|
| 1. | Symptoms are usually caused by sensitiveness to a substance as it exists naturally. | The patient often appears sensitive to a product after alteration within the body. |
| 2. | Symptoms usually appear soon after exposure to the offending agent. | Reactions are frequently delayed. |
| 3. | Skin tests made with extracts of the offending agents are usually positive and appear immediately. | Skin tests are often negative or indefinite and delayed reactions are common. |
| 4. | Relief usually follows avoidance of the agent. | Avoidance of case is often so difficult of accomplishment that this method of treatment fails. This may be accounted for possibly by assuming that here we often have sensitiveness to agents common to many articles. |
| 5. | The symptoms can usually be relieved by specific treatment with the agent to which the patient is sensitive. | Specific therapy often fails. |
| 6. | Symptoms, as a rule, are not markedly affected by nonspecific protein therapy. | Nonspecific protein therapy is rather frequently beneficial. |
| 7. | Symptoms are frequently not completely relieved by small doses of epinephrin subcutaneously. | Small doses of epinephrin (¼ c.c.) are very likely to give relief. |

A comparison of contact (or local reactions) and general reactions.

## Time and Duration of Reaction

The time interval between exposure and reaction varies greatly—in fact, varies from a matter of seconds to a matter of hours or even days. When sensitiveness is great and exposure intense, the reaction, as a rule, occurs quickly. This statement, however, is subject to exception. In a patient sensitive to egg, the reaction, asthma, could be brought on by almost infinitesimal quantities of egg but the symptom would never appear within less than forty-eight hours after contact with egg.

Contact reactions are usually prompt and over quickly. In general cases, the reaction is often delayed for hours or even for days. In the latter case, the duration of the reaction is likely to be long. In one patient, the source of whose illness was not discovered, the reaction, hives and angioneurotic edema, did not appear for ten days after the use of intracutaneous tests and lasted almost one week. The illness resembled serum sickness and may have been serum sickness.

Delayed reactions make specific diagnosis difficult, especially in the case of sensitiveness to more than one agent.

## Intensity and Variation in Reactions

The severity of a reaction is dependent upon two factors: degree of sensitiveness and intensity of exposure. Contact reactions can vary from slight erythema, itching, and edema to local gangrene. General reactions can vary from a slight feeling of weakness to total collapse and death.

The result of frequently repeated mild reactions is usually quite different from the manifestations of occasional severe reactions. The former is more likely to result in structural tissue changes while the latter usually leaves the tissues normal. For example, in the case of the skin an acute severe reaction usually manifests itself as erythema, edema, or itching which disappears after a time, leaving the skin normal in every respect, while frequent mild reactions may result in thickening of the skin, desquamation, and cracking. In Koessler's cases of chronic asthma frequent reaction resulted in hypertrophy of the muscles of the bronchi. The usual nasal reaction sneezing, swelling of the membranes, and secretion of clear mucus is of little practical moment when continuing over a period of a few days, or even weeks or months, whereas slight perennial reaction continuous over a period of years usually results in polyps.

The degree to which patients react does not vary greatly in contact cases. It tends to vary, however, from time to time in the general cases. In contact cases symptoms may remain remarkably constant for years, variation depending almost entirely upon variation in the intensity of exposure. In general cases, however, the degree of sensitiveness appears actually to vary or perhaps, better expressed, the degree of reaction upon a given exposure varies. Such variation can be accounted for in food cases by assuming that under certain circumstances split products to which the patient reacts are either not liberated by the digestive juices or if liberated, are not absorbed.

It has been mentioned previously that under normal conditions, if animals are fed on a fat, starch, or protein free diet, the pancreatic juice loses a large proportion respectively of fat, starch, or protein splitting ferment. When the animals are again fed a diet containing these foods, the respective enzyme is again elaborated in quantities required by the diet. Such variation, occurring under natural conditions in the digestive juices in human beings must have its effect both upon foods and digestive products and in this

way, might cause variation in the intensity of contact between patient and the product to which he reacts. This may also account for the relief which frequently follows a radical dietary change.

Further than this, the mucous membrane of the gastrointestinal tract varies from time to time in its ability to absorb products which are useful and in its ability to exclude products which are noxious. Such changes occur under the influence of chronic diseases, such as gall bladder disease, chronic appendicitis, ulcer, ptosis, adhesions, atrophy, and the well-known condition, tabes mesenterica. It is not only possible but it seems likely that under certain conditions, noxious products, even histamine, which are ordinarily excluded are absorbed and cause reaction.

Whatever the explanation of variation in reaction may be, certain it is that at times reactions vary without evident cause and in most extreme degree. Asthma under the influence apparently of the same irritant may vary in degree from a slight tendency to cough to dyspnea so severe as to result in cyanosis, emphysema, and a condition bordering on coma. Hives may vary from small punctate elevations of the skin to large flat geographically shaped areas or to subcutaneous swellings which, if located on the face, may completely obliterate the features. The variation frequently occurs without apparent cause, rhyme, or reason. However, the more complete the study of a case, the rarer become these apparently inexplicable changes and once a case is thoroughly solved, reaction appears more and more to be absolutely obedient to law.

## Periodicity of Symptoms

Periodicity is the rule rather than the exception in illnesses caused by allergy. Symptoms frequently occur at yearly or seasonal intervals and frequently at twenty-four hour intervals with great regularity and less often at monthly intervals. Twelve-hour intervals are less common. In one case, attacks occurred at about four-hour intervals for months. In another, at exactly seven-day intervals for a period of almost ten years. Some attacks occur at irregular intervals. In one case, asthma alternated with attacks of exophthalmic goiter at irregular intervals for several years. In several instances, reactions have occurred only during pregnancy and in one case, the patient enjoyed relief from chronic urticaria during pregnancy.

Periodicity can often be accounted for by the fact that exposure to foreign agents is frequently periodical. Also, by the fact that many factors which secondarily influence symptoms are frequently met with periodically. Patients subject to physical allergy, to be described subsequently, have periodic variation in symptoms because of variance in intensity of exposure to a physical agent, such as light, heat, cold, and exercise. As will be shown subsequently, night reactions are frequently temperature reactions occurring in cold or heat sensitive cases—in the former when the patient is exposed to cold air and in the latter (heat sensitive cases) most markedly between two and six in the morning when the body temperature is inclined to be lowest.

Case 7.—*Nasal Reaction Occurring at Seven-Day Intervals.*—An interesting example of periodicity is that of an army officer who, during a period of some ten years, was subject to one attack of nasal reaction each week. It occurred so regularly for several years that regardless of environment or habit, the patient could actually count on an attack every Thursday morning starting soon after breakfast. Additional attacks of short duration were occasionally brought on by a blow on the nose and occasionally attacks would fail to appear on schedule when the patient was under intense excitement, such as being under shell fire, or while playing polo. Nothing was found to account either for reaction or its periodicity except an opaque right antrum. It is thought possible that complete filling of the antrum with secretion might be responsible directly or indirectly for the outbreak of symptoms and that the cavity might be emptied during an attack with temporary relief. It hardly seems possible, however, that refilling could occur with such regularity over so long a period of time and under such remarkably varied conditions as those under which an officer lives.

He was observed during an attack which was characterized by sneezing and a profuse discharge of clear mucous secretion from the nose. The discharge injected intracutaneously was without apparent effect as were other intracutaneous tests. The antrum was drained by operation but relief did not follow.

While periodic variation in symptoms seems at times mysterious and without apparent cause, close study reduces the mystery. Heat and cold sensitive cases to be described subsequently are each worse during cold months and on cold days and at night when body temperature is subnormal.

Cases affected by posture are inclined to be worse at night, as are patients sensitive to feathers and other articles with which they come in contact about the house. Once the source of an apparently mysterious reaction is discovered, it is usually found that the symptoms in their periodicity are consistently obedient to law.

## Transmutation of Symptoms

Symptoms of allergy frequently change in character, intensity, and location. Transmutation in character is interesting and may occur quickly or slowly and in slight or in marked degree. This phenomenon is difficult to explain. Hives may disappear spontaneously or under treatment only to be followed by angioneurotic edema in other areas or by asthma. In two cases of intensive hive reactions, the applications of a thick suspension of soda to the skin was followed by reduction in the intensity of itching but was followed within a few seconds by marked angioneurotic edema in other areas, together with angioneurotic edema of the larynx. One case of urticarial dermographia in which the eruption had been confined for years to the body and extremities with freedom of the face, and feet under treatment (by frequent scratching of the skin with a stiff brush) involved, for a time, chiefly the face. Later, the condition was greatly reduced in severity under the influence of the same treatment. In several patients hay fever relieved by specific pollen treatment was followed by asthma and vice versa. Autumnal hay fever treated successfully with pollen extract was followed by clinical sensitiveness to fruits, animal hair, or spring pollen in several instances. In one case, fall hay fever relieved completely by fall pollen treatment was replaced by spring hay fever. General eczema without treatment may disappear to be followed by asthma. General pruritus in several instances has alternated with attacks of asthma. In one case, Ménière's syndrome had a tendency to alternate with asthma, and in one case convulsions alternated with asthma. In one case, severe allergic headache disappeared to be followed by chronic asthma. These weird transmutations are relatively common and very definite.

## Sensitiveness and Tolerance

A patient is not made ill by all the agents to which he is actually sensitive and to which he gives positive skin tests—in fact, as a rule, he is actually made ill by relatively few of them. It is not uncommon to find that a patient who gives strong positive skin tests (large wheals with pseudopods) to fifty or more substances on intracutaneous injection, is actually made ill by only one or two of them as encountered under natural conditions. This is no doubt

very often due to the fact that the substances to which he reacts cutaneously cannot penetrate the skin or mucous membranes and give rise to a reaction and in the case of foods, because they are frequently altered by digestive processes or putrefactive bacteria before they reach areas in the intestine from which they can be absorbed in quantities sufficient to cause reaction. In addition to this, however, patients no doubt have a relative tolerance for a great many substances to which they are actually sensitive and do not react unless large quantities of the substances are encountered.

Tolerance may be given to patients who are sensitive to foreign agents by treatment with graduated and gradually increasing doses of the agent to which they react. This will be discussed fully in a subsequent chapter. However, at this point it may be said that patients who react violently to small doses of a pollen can be made so tolerant of the pollen through the effect of treatment with graduated doses that they can eventually tolerate ten thousand times as much as that which would have produced reaction before treatment was commenced. The fundamental reason for this is not altogether clear. Tolerance for protein in sensitized animals can be accounted for by assuming that through graduated doses the precipitins of the blood can be neutralized so that further introduction of antigen finds nothing with which to react and is, therefore, harmless. Zinsser and others are inclined toward the view that in human sensitiveness, the reacting antibodies are attached to the tissue cells. If this is true, tolerance might be accounted for through assuming that by graduated doses of the agent to which a patient reacts, the receptors are saturated so that further introduction of the agent produces no visible effect.

Whatever may be the explanation, the facts in the case somewhat resemble those observed in human beings with tuberculin sensitiveness and tuberculin tolerance. Human beings cannot be rendered sensitive to tuberculin by the intracutaneous injection of tuberculin. They can be rendered sensitive, however, by infection with tubercle bacilli so that upon inoculation with small quantities of tuberculin (harmless to normal individuals), they react with symptoms of greater or less severity. A patient so sensitized can be rendered tolerant of tuberculin through administration of graduated doses so that eventually the administration of enormous doses is without apparent ill effect.

Likewise, it seems difficult or impossible to sensitize a patient to pollen. Of the thousands upon thousands of substances which have been injected intracutaneously in my office, I do not know of one solitary example of sensitiveness produced by it—in fact, the only instances of sensitiveness produced artificially which have come to my attention have followed the use of repeated doses of salvarsan. Patients, however, with a positive family history, can become spontaneously sensitive to foreign substances due, apparently, to natural contact. Once sensitive, they can be given tolerance by subcutaneous treatment. Furthermore, I feel sure that in many instances natural tolerance is gained through frequent gross contact. I believe it is for this reason that patients rarely react to substances which they encounter frequently in gross amounts. I have not found one solitary example of sensitiveness to the grosser constituents of beef or to the grosser constituents of any of the commonly eaten foods. Patients sensitive to milk, egg, or beef, as a rule, react to one of the smaller constituents, and it would seem because of the fact that such patients often avoid the agents to which they react, they have little opportuntiy for gaining tolerance. This has been discussed at length in a previous chapter.

## CHAPTER XIV

## SYMPTOMS OF REACTION

### General Symptoms—Shock

Local or contact reactions, such as hay fever, are usually accompanied by slight manifestations of general reaction, such as eosinophilia. This is due apparently to the absorption of a small amount of substance which offends locally. When a patient is excessively sensitive or when exposure is intense or when the local reaction covers a large area, the general reaction may be severe, but rarely alarming. This is fortunately rare. In my experience, it has occurred in rare instances after natural contact with animals, with fish glue, after the handling of fish, after the ingestion of foods or drugs to which the individual is hypersensitive, and after subcutaneous, intravenous, and intracutaneous injections and even after scratch tests. Typical illustrations of general reactions which are severe are those which occur at the beginning of or during a blood transfusion, during or soon after the injection of therapeutic sera or pollen extract or drugs, or after insect bites in excessively sensitive individuals.

With the onset of reaction, the patient usually complains first of generalized itching followed within a few moments by pain in the top of the head or pain in the lower spine or both and within a few moments by a feeling of total collapse in which they think they are going to die. Pain in the back and head may become so severe as to cause the patient to cry out. General erythema and itching becomes intense. The face and tongue may swell and the patient becomes slightly or markedly asthmatic. Blood pressure usually drops and may reach an extremely low level. The pulse becomes weak and compressible and occasionally almost imperceptible. Upon appropriate treatment with adrenalin and intravenous injection of caffein, if indicated, recovery is usually prompt and complete—in fact, every case of shock which I have observed has recovered promptly under this medication. Severe reactions untreated, usually show improvement within thirty minutes. In some cases, however, which come on slowly, especially if the reaction is

delayed for one or several hours or days, it may last a number of hours. In the latter case, hives and angioneurotic edema usually dominate the situation and the condition resembles serum sickness.

Whereas I have seen many alarming reactions, as above described, and all recovered promptly when suitably treated, one which I saw in consultation in 1912 after a therapeutic dose of antitoxin had been administered did not recover. This was before the day when reactions were understood as now and before the advent of effective ways of administering adrenalin. The patient was evidently a horse sensitive case and a few moments after the injection of antitoxin, had a chill followed by collapse. When I saw her a short time afterward, she was too weak to talk or even raise her hand. Adrenalin was used in therapy but not in sufficient dosage—so that it failed to relieve her.

In a case of pernicious anemia previously described the patient proved to be hypersensitive to milk, a donor was used whose blood was compatible so far as iso-agglutinins were concerned but who, in preparing himself for transfusion, drank a quantity of milk. This patient reacted after the injection of one syringe of his blood to such an extent that within less than one minute she was apparently lifeless. She had all the symptoms previously described and was relieved promptly by the free use of adrenalin. During an experience with over six hundred blood transfusions, I have observed only two severe reactions of this kind.

Another case of severe reaction was that of a patient to be described subsequently whom we thought from his story was sensitive to fish glue. He was tested by the application of a little glue to a scratch on the skin. The glue was washed off after a few moments, but in spite of this he reacted almost as violently as the transfusion case just mentioned.

Several cases of death have been reported from reactions such as the above following the injection of as little as one drop of normal horse serum intravenously following the use of prophylactic dose of diphtheria antitoxin and the injection of .01 c.c. of a solution of fish glue intracutaneously, and even following the intravenous injection of one or two syringefuls of blood by transfusion, even blood from donors proved compatible so far as iso-agglutinins were concerned.

Whereas I have had early in my experience several very severe reactions following the therapeutic use of such agents as arsphenamine intravenously, pollen injections subcutaneously and intracutaneously, twice at the beginning of a blood transfusion, once after the application of fish glue to the skin, and once after the application of Wright's wood smoke to the skin. I have learned to avoid them so that during the past two years I have had only one severe reaction. This I attribute to strict attention to the precautions to be mentioned in the subsequent chapters.

One cannot conceive of the sudden stormy nature of constitutional reactions unless he has observed them. Such occur frequently in natural life due to accidental contact with agents to which patients are excessively sensitive. I am sure it is responsible for a relatively large proportion of cases of sudden death in apparently healthly individuals which are classified by physicians and coroners as "cause unknown" or "heart failure," "embolus," "hemorrhage," or "status lymphaticus." It is not uncommon to hear of individuals in apparent health after a hearty meal having an attack of nausea, vomiting, pain, collapse, and death within a few minutes. The dangers to which sensitive cases are subjected are illustrated by the case which follows.

CASE 8.—*Severe Shock Caused by Fish Glue.*—The patient, a man of fifty-two gave a negative family history of allergy so far as he knew.

He had himself been subject to asthma the year round for three years, most severe in the fall. He had been subject to hives, to angioneurotic edema, and frequent urination off and on since childhood. He had suffered very severe illnesses several times after contact with glue. Two of these illnesses, which followed the licking of a postage stamp, were characterized by swelling of the tongue and lips, generalized redness of the skin, itching, hives, angioneurotic edema, and finally, collapse which lasted about one hour. He had learned to keep away from glue. Upon one occasion he picked up a beer bottle with a wet lable and an attack followed similar to, though less severe than the one described above. He had an attack once after picking up a fish, and on another occasion, after putting on a pair of shoes which had recently been repaired. Within a few moments, he realized that a severe attack was starting. He took off the shoes in great haste, but not soon enough to prevent an attack, associated with asthma, hives, angioneurotic edema of the feet, generalized redness of the skin, and collapse.

With this history I realized that the patient was extremely sensitive to glue and made my tests with the greatest of care. He was tested with all the common foods, pollens, animal hair, etc., and gave marked reactions to a great many of them, most marked to egg. He was later tested by the application of LePage's glue to a scratch on the skin. An area of erythema soon appeared

and the glue was immediately washed off. Within a few moments a large hive appeared around the point at which the glue was applied, the patient turned red, began to cough, wheeze, and was laid down on a table. His blood pressure dropped to practically nil and he said he felt as though he were dying. He had the most severe reaction which I have ever observed except one which occurred during a transfusion, and we believe this attack would have terminated fatally had it not been for the speedy use of atropine sulphate, 1/150 grain, and several doses of adrenalin. After relief from this attack he had a recurrence in about one hour, which was again relieved with adrenalin. Following this, he recovered completely and suffered apparently no further ill effect from the reaction.

Through the avoidance of eggs and the removal of glue from his house (labels, books, stamps, etc.) he has been almost completely free of asthma.

Whereas stormy symptoms, such as those just described, are observed occasionally, the milder symptoms of reaction are every day occurrences and bring patients to doctors' offices with varying complaints probably as often as any other illness. The milder reactions include one or many of the symptoms to be described subsequently.

### Orbital Symptoms

These include puffiness and itching of the lids, slight redness of the lid margins, edema of the conjunctivae, increased lacrimal secretion. This reaction may vary in intensity from slight itching of the lids to edema which may nearly close the orbital apertures. When it occurs alone or is associated with nasal reaction, it is almost always the result of surface contact with some offending agent. Ocular reactions occasionally occur as part of a general reaction, however. This is often the case when swelling is gross and when the skin of the face is also involved.

Severe reaction may simulate nasal sinus infection or even sinus thrombosis but can be easily differentiated from them by the absence of fever, leucocytosis, tenderness, and often by the presence of other general manifestations or reaction.

### Nasal Symptoms

Sneezing, pale swelling of the mucous membrane of the nose associated usually with excessive watery or clear mucous secretion are the usual nasal symptoms. This reaction may vary from slight annoyance to complete stoppage of the nose associated with an outpouring of secretion which may drench towels. It is occasionally associated with frontal headache caused by pressure in the nasal

sinuses or by pain in the top of the head occurring as a direct result of general reaction.

Nasal reactions occurring alone or associated with coryza or bronchial asthma suggest reaction of surface contact with an air-borne substance. Nasal reactions rather frequently occur, however, as part of a general reaction, in which case they are likely to be associated with other symptoms of general reaction.

Nasal reactions are prone to occur in patients subject to general reaction who have sinusitis or bad mechanics in the nose. In this case, the allergic element may not be apparent and can easily be overlooked. Furthermore, chronic edema of the nasal membranes caused by allergy predisposes to sinus infection and makes worse obstruction due primarily to bad mechanical conditions.

Chronic edema of the mucous membrane in perennial cases frequently results in polypi (in 24 per cent of cases). In patients having multiple polypi, chronic allergy must be suspected first and foremost as the primary etiologic factor. It is unusual, however, to find polypi in uncomplicated seasonal cases (about 6 per cent of cases). The presumption is that the duration of edema in seasonal cases is too short to give rise to this result.

The above facts are important from the standpoint of local treatment, for in the case of nasal reaction, local treatment, especially surgical treatment, does not reach the root of the evil and often does much more harm than good.

The above statements do not apply to polypi occurring in one cell or one group of cells. In this case, infection is the more common cause.

### Pharyngeal and Oral Symptoms

Itching of the soft palate and pharynx, cough, less commonly edema of the uvula and soft palate and swelling of the tongue are the usual oral and pharyngeal symptoms. This may vary in severity from slight annoyance to intense itching and even to swelling of the soft palate which may seriously obstruct respiration and require drastic measures for relief. The milder reactions occur frequently as a result of surface contact. The more severe reactions, associated with edema are usually the result of constitutional reaction.

The condition can be easily mistaken for infection unless the general characteristics of this type of reaction are borne in mind.

### Laryngeal Symptoms

These include cough, hoarseness, pale edema of the membranes of the larynx and epiglottis. This may vary in severity from simple hoarseness and cough to edema which may embarrass respiration and require tracheotomy. In one case of reaction of unknown origin which I saw in consultation, swelling of the epiglottis and false cords reduced the size of the passage to such an extent that it would hardly have admitted a body the diameter of a match. Before tracheotomy could be performed the patient nearly died of asphyxia. The day following operation, the edema disappeared completely, the tracheotomy tube was removed, and the patient has remained well since.

Slight reactions are commonly the result of surface contact, while the more severe ones associated with edema occur more commonly as part of a general reaction.

The condition can easily be mistaken for retropharyngeal abscess or perichondritis. The absence of local redness and the history usually serves to differentiate.

### Bronchial Symptoms

These include cough, bronchial obstruction with inspiratory and expiratory wheezing due apparently both to edema of the membranes and to spasm of the bronchial muscles, and the expectoration of clear, watery or mucoid sputum rich in eosinophils and often containing Charcot-Leyden crystals. This reaction may vary in severity from slight cough and shortness of breath on exertion to obstruction so complete as to cause acute emphysema, spontaneous pneumothorax, and even a condition bordering on asphyxia. Patients may become comatose with the color of slate from asthma. Death from asphyxia, however, is rare in uncomplicated cases—in fact, the only cases of asthma which I have observed which terminated fatally were complicated with bronchopneumonia or other illnesses.

Bronchial symptoms are probably as often due to surface contact with offending substances as to agents distributed by the blood stream. Contact reactions are frequently associated with reactions in the orbit, nose, or pharynx, whereas asthma as a general symptom is usually associated with hives, angioneurotic edema, or other

general manifestations. Asthma may occur, however, as an almost isolated symptom.

The symptoms and the course of asthma are so varied that many pages would be required to even approach a complete story. Little would be gained by such a description. Suffice it to say that the symptomatology of asthma is as varied as the symptomatology of urticaria. The variation in both instances is not a matter of accident but a matter of law, the symptoms appearing whenever the conditions are met with, which produces them and disappearing when such conditions are avoided. Cases of asthma of long standing are usually complicated by anatomic changes in the mucous membrane and musculature of the bronchi; in the mucous glands, in the lung parenchyma, and even in the shape of the chest itself. Furthermore, in cases of long standing, infection both in the mucous membrane of the tubes and parenchyma of the lung itself complicates the situation so that chest symptoms often persist even after the agent primarily responsible for the disorder "asthma" is eliminated.

The seasonal attacks and short periodical attacks are of little consequence as compared with the perennial cases in which symptoms persist for weeks, months, or years. In periodical cases, the pulmonary tissues apparently have a chance to regain their normal status between attacks. Cases in which the symptoms are inclined to be continuous fare much worse. The most serious cases are apparently the winter cases, and of these, I am sure many are heat sensitive cases. They are predisposed to influenza, suffer severe exacerbations following such attacks, and frequently end up with apparent bronchopneumonia. In a number of instances, I have known patients of this kind to have as many as three or four attacks of "bronchopneumonia" each winter. Every case of death which has come to my attention which could be attributed to asthma, has terminated in this way.

Nothing is simpler than the diagnosis of asthma in a well-marked case. The finding of musical râles through the chest with negative x-ray findings combined with a positive family and personal history, leaves little chance for error. However, mild cases in which the symptoms may be simply cough and shortness of breath on exertion, are often difficult to diagnose and are frequently misdiagnosed tuberculosis, emphysema, chronic bronchitis, or bronchiectasis. They

are often believed to occur as a result of a nasal defect, chronic nasal sinus infection, heart disease, kidney disease, or enlarged thymus. Many cases of cough complicating the latter illnesses are, in reality, true bronchial asthma.

There are few diseases more disagreeable than chronic asthma. It frequently results in real organic pathology, such as chronic bronchitis, emphysema, fixed chest, and in severe cases, emaciation. I have not observed one case terminate in bronchiectasis, however, except when complicated by other conditions.

In treating asthma, it is essential not only to treat this condition, but the complications and sequelae. It is all important to get rid of the cause, if possible, and in addition to this, to use every means at our disposal to keep the patient free of symptoms. As a general rule, the longer the patient stays free of symptoms, the easier are the recurrences to treat. This will be discussed at length in a subsequent chapter.

### Gastrointestinal Symptoms

The most interesting of the abdominal symptoms is abdominal pain which may be either mild or severe, acute or chronic, local or general, steady or griping. It is often related to the eating of food and quite frequently appears a few moments after the ingestion of some particular food. The latter history always suggests that the reaction is a result of local contact. The pain may be as severe as that caused by almost any other acute abdominal condition and may cause the patient to writhe in agony. Whereas acute pain is a striking symptom, milder and more chronic pain is commoner. Other alimentary symptoms of interest are abnormalities in the quantity and acidity of the gastric juice, nausea, vomiting, bloating, diarrhea, and mucous stools.

Symptoms as described above may vary in gravity from simple discomfort to pain so severe as to cause collapse, and to chronic nausea, vomiting, and diarrhea which can cause emaciation in highest grade.

CASE 9.—*Emaciation Caused by Hypersensitiveness to Foods.*—One of the most marked cases of emaciation which I have observed was in a patient with alimentary allergy who was sensitive to almost all the common foods. The patient, because of abdominal pain, nausea, vomiting, and the fear of pain on eating had been reduced in weight to less than seventy pounds. During her illness, gallstones were found and removed at operation without relief. Several weeks

after operation when the patient was on the verge of death from starvation, she was found sensitive to practically every common food except the meats and fruits. On a diet confined to meats and fruits, she gained weight at the average rate of almost a pound a day until at the end of two months, she actually weighed over one hundred and thirty pounds. During this interval, an effort was frequently made to add to her diet some of the vegetables, cereals, milk, and eggs but always with recurrence of abdominal pain, nausea, and vomiting which would last several hours. It seems almost inconceivable that a person could gain weight on such a diet, but this was actually the case.

Abdominal symptoms may simulate those caused by other illnesses, but rarely simulate them perfectly. They need not be mistaken for them by careful physicians who recognize the existence of this condition. It can be easily differentiated from acute inflammatory lesions by the lack of fever, leucocytosis, and the absence of marked tenderness or muscle spasm. Furthermore, an eosinophilia and a personal and family history of other allergic conditions can usually be found.

Alimentary allergy is prone to occur in individuals who have organic lesions in the alimentary tract or its appendages—in fact, in more than 50 per cent of the cases which have come under my observation some definite organic disease, such as chronic appendicitis, gallstones, dense adhesions, extreme ptosis, or ulcer, has been found. Relief of these lesions by treatment has occasionally been followed by relief of sensitiveness but this result has been by no means constant. It seems probable that in patients with allergic tendencies a definite pathologic lesion in the alimentary tract tends to focus the illness in this locality.

Further than the above, acute inflammatory reactions which necessitate surgery occasionally follow severe attacks of alimentary allergy. In several instances it has initiated an attack of acute appendicitis or gall bladder disease. This is not to be wondered at when we consider the turmoil which can occur as a result of reaction with symptoms such as edema of mucous membranes, severe contraction of nonstriated muscle, and increased secretion. Either factor in severe grade would be prone to exaggerate an illness caused by organic disease, and result eventually in an acute inflammatory process.

It is a common history for acute diseases in the gall bladder or appendix to occur several days after the eating of a food which causes nausea, vomiting, pain in the epigastrium, and possibly

diarrhea. This is a frequent result, I am sure, when sensitive patients having mild abdominal disease, such as stone in the gall bladder or appendix, encounter a food or other substance to which they react.

Physicians who doubt that allergy is an important inciting cause of serious inflammatory disease in the abdomen must, if consistent, doubt that edema and anemia of mucous membrane, associated with violent peristalsis, and increased secretion can initiate or augment an inflammatory process.

Case 10.—*Alimentary Reaction followed by Appendicitis.*—The patient, male, aged twenty-five, ate shad roe from two to five times a week at lunch for a period of several months. After removing to another locality, he did not eat shad roe for a period of about two years. He then became subject to occasional attacks of severe nonradiating, steady pain in the epigastrium which would develop about fifteen minutes after a meal, and last from three to five hours. Occasionally, the pain was associated with nausea and vomiting. The pain was so severe as to completely incapacitate him for mental or physical work. Several attacks were followed by tenderness over the appendix with slight fever and leucocytosis which lasted for about a week. The case was diagnosed recurrent appendicitis and the appendix was removed. A few adhesions about the appendix were found, together with several concretions in its lumen. Similar attacks of epigastric pain occurred after removal of the appendix. They differed from the former attacks only in the fact that they were not followed by tenderness in the right iliac fossa. Finally it was discovered that the attacks occurred invariably after the eating of shad roe and that when shad roe was eliminated from the diet no such attacks occurred.

This sensitiveness persisted for more than ten years but gradually became less severe in grade. The ingestion of shad roe at the present time causes discomfort in the abdomen and nausea, but not severe pain.

Physical examination of the patient disclosed nothing of interest except a moderate grade of ptosis.

An intracutaneous injection made with an aqueous extract of shad roe gave rise to typical hive about about 0.5 cm. in diameter.

Case 11.—*Chronic Alimentary Allergy in a Patient with History of Gallstones and Appendix Abscess.*—The patient was a woman, aged forty-five. Her father had autumnal pollen-asthma until his death several years ago. Her brother, because of summer and autumnal hay fever and eczema was forced to leave this climate.

*Previous Illness.*—The patient did not give a history of hay fever, asthma, eczema, or other symptoms of allergy. Eight years before seeing me she developed an appendix abscess which required drainage. Several years later she had an infected gall bladder which required surgical removal. One year after this, for the first time in her life, she became subject to chronic dyspepsia, the outspoken symptoms of which were severe steady pain in the epigastrium

associated with nausea and vomiting which would come on every day about one-half hour after eating, and last from one to three hours. She found by experience that the pain was relieved to a certain extent by lavage. The patient had been dieted and treated without relief for several months before coming under my observation. The history was otherwise negative or of no interest in this connection.

*Physical Examination.*—On examination there was found a slight grade of oral sepsis, slight general abdominal tenderness, high grade ptosis, adhesions about the pyloric end of the stomach very evident on roentgen examination and a bulb deformity, due evidently to adhesions. Examination was otherwise negative or of no interest.

Careful dietary and intracutaneous tests proved the patient to be sensitive to milk, beef and egg white. Intracutaneous injection of the proteins mentioned gave rise in a few moments to typical wheals about 0.5 cm. in diameter. Subcutaneous inoculations with small amounts of milk, egg white, and beef serum, used subsequently in therapy, frequently gave rise to attacks of abdominal pain and vomiting similar to those of which the patient complained originally. The ingestion of a small amount of beef, milk and egg white, taken as a clinical test during a well period in each instance gave rise to attacks of abdominal pain and vomiting, which came on within less than one-half hour and lasted from one to three hours. Other foods tested in this way caused little or no distress when she was on a diet free of egg, milk, and beef.

The patient was treated with subcutaneous inoculations of beef serum, milk, and egg white (increasing from 0.001 mg. to 1 mg.) over a period of two months. She did not at any time during this treatment have hives, asthma, or other cutaneous or respiratory symptoms of reaction. A number of reactions, however, confined her to bed several hours with abdominal pain, vomiting and general malaise.

At the end of two months her sensitiveness had been reduced to such an extent that she was tolerant of the small amounts of milk and eggs used in the cooking of ordinary foods, so that she has been able since treatment to live in comfort on an ordinary diet when she simply avoids the drinking of considerable amounts of milk and the eating of eggs or beef.

## Cutaneous Symptoms

Cutaneous symptoms, like nasal and bronchial symptoms, may be acute or chronic, seasonal or perennial, in character. This depends upon the nature of substance to which the skin is sensitive. The symptoms pruritus, erythema, and edema may occur together or singly and may be associated with the exudation of sebaceous or watery secretion. Marked thickening of the skin is common in the more chronic cases and may be associated with desquamation and cracking of the skin. Skin reactions may be mild and consist of a simple slight pruritus and erythema, or may be most severe and

when the skin of the face is involved, may almost obliterate the features and transform it into a swollen, red, greasy, weeping, unsightly surface. Itching may be almost intolerable and secretion may drench the hair and clothes in severe cases.

Dermatitis may occur as a result of contact with the air-borne substances or may occur as a part of a general reaction. Dermatitis confined to the face, neck, hands, and to lesser degree the ankles (that is, to the exposed parts) is almost always a result of surface contact whereas generalized dermatitis and even dermatitis, occurring in patches over the body generally, is more frequently the result of a

Fig. 58.—Typical contact reaction of the face. Dermatitis confined to the exposed parts caused by local contact of the skin with air-borne substances. The skin test in a case of this type is likely to resemble that shown in Fig. 65.

general reaction. This statement is, of course, subject to exception. In three cases of wool sensitiveness the reaction was quite general, due to large areas of surface contact with woolen underwear.

Contact reactions of the skin are not common. One of the earliest cases reported was Sutton's caused by ragweed pollen. Dermatitis frequently is traceable to sources of vegetable origin, other than pollen, just as in the case of nasal and bronchial reaction. Interesting reactions are those which are caused by formalin and other chemical irritants, drugs of the cocaine series, hair tonics, dyes, gasoline fumes, and by smoke. These occasionally cause dermatitis,

the source of which is difficult to discover unless the physician can visit and study the premises on which the patient lives. On several occasions I have examined patients who have become completely well while visiting Kansas City and have had recurrences on returning to their homes or places of business. In one patient, an undertaker, the source of illness was traced directly to his shop, but it was apparently impossible to find the actual offender. He could work in other undertaking establishments and remain symptom free.

Contact symptoms are frequently associated with nasal or bronchial reaction. Unfortunately, reactions are frequently delayed. This makes diagnosis difficult. Skin tests are frequently uncertain and in the case of delayed reactions, may amount to little more than redness which may be confined to the area directly exposed to the irritating agent. The reaction shown in Fig. 65 was caused by the application of the bloom of a ragweed to the patient's arm. Each of the small round areas, I believe, occupied the site of a pollen granule. These later coalesced in the center of the area to form a large, red, desquamating surface. The reaction which followed the intracutaneous injection of ragweed extract was insignificant as compared with the one shown in the illustration and did not extend markedly beyond the area directly treated with the extract. This is emphasized because of the fact that skin tests made in the usual way in this type of illness may give positive results which because of a lack of a tendency to spread can be completely overlooked. I know of no illness more distressing than a contact dermatitis of the face and hands or of a type of reaction which is more difficult to trace to its primary source.

Dermatitis which occurs as part of a general reaction may appear as erythema, pruritus, dermatitis, urticaria, or angioneurotic edema. Since the latter two conditions are really not primarily cutaneous but subcutaneous, they will be dealt with subsequently under these headings.

In dealing with this subject clinically, one must not forget the part played in many cases by specific sensitiveness to the action of physical agents to be described subsequently. This, I believe, is one of the commonest sources of reaction of the sort.

Whereas the symptoms as mentioned have been emphasized, the fact that skin reactions may be either vesicular or papular, must be mentioned. Furthermore, the fact that solitary reactions can

occur and give rise to very confusing pictures must be emphasized. This portion of my work is not dealt with in more detail because of the many unknown factors which must be left for further investigation.

### Erythema, Pruritus, Urticaria, and Angioneurotic Edema

These four conditions, when they occur as a result of hypersensitiveness, seem fundamentally examples of one pathologic process. Erythema and pruritus are commonly associated together and would appear frequently to be a result of capillary dilation. In many patients the usual reaction, erythema and pruritus, is associated with hives of varying size when the reaction is unusually severe. Hives, under certain conditions, may be associated with or alternate with angioneurotic edema. Transmutation, one to the other, may occur spontaneously or under the influence of therapy.

Urticarial lesions vary greatly in distribution, size, and shape. They vary from small linear or pin-point lesions to large, irregular, flat areas which may take on almost any conceivable shape. In the case of large reactions (giant urticaria) huge skin surfaces may be involved and give rise to marked deep swellings which are ordinarily classed angioneurotic edema. The size and shape of the hives are influenced, no doubt, largely by the tissue spaces and elasticity of the tissue layers in which they are located.

Angioneurotic edema may appear at any area of the skin surface and in the internal organs. When it causes obstruction to some important channel, such as the trachea or small intestine, very serious disturbances and even death may result.

The four symptoms above described present different clinical pictures, varying according to the cause of the illness. Reactions caused by the ingestion of a food which is rarely eaten, are usually of short duration, but may be severe while they last. If due to an article commonly met with, the illness is chronic and may last for weeks or months or even years.

Urticaria of the deep variety and angioneurotic edema is not often a reaction of surface contact. It occurs more frequently as a part of a general reaction. It occurs typically after the ingestion of foods to which a patient is sensitive, typically after the injection of therapeutic sera, or of pollen extract, and after insect bites in sensitive individuals. The reaction may appear without apparent

cause in chronic diseases, such as carcinoma, intestinal disorders, chronic interstitial nephritis, and as a complication of the acute infectious diseases, such as acute tonsillitis and rheumatic fever. On the basis of the work of Eustis and Koessler, one can easily believe that it occurs frequently as the result of the absorption of histamine-like bodies from the intestinal tract and in this case, might involve normal individuals as well as individuals of allergic strain.

Fig. 59.—A typical manifestation of a general reaction. Angioneurotic edema of the hand caused by the ingestion of foods to which the patient was sensitive.

In this connection, one must emphasize the importance of physical agents to be described subsequently as a cause of reaction of this type—not only of erythema, pruritus, and urticaria, but also of angioneurotic edema. In a number of cases studied, urticarial lesions could be traced specifically to the effect of a physical agent, such as heat or cold.

It is furthermore necessary to mention the importance of solitary reactions which were occasionally observed and which may appear as wheals or papules under the influence of agents whose effect is too mild to provoke widespread general reaction.

## Headache

Headache may occur as a primary symptom of reaction or may be the result of a pressure in the nasal sinuses caused by swelling of the nasal membranes. The latter type could hardly be called a primary allergic headache.

Headache due primarily to allergy is not a common symptom but makes up in severity for its rarity. It may be so severe as to cause the patient to cry out in agony in spite of the use of relatively large

Fig. 60.—Typical example of a solitary reaction. Wheals caused by exposure of the skin of the elbow to light for a few seconds. A longer exposure (2½ minutes) of the same skin area would cause the entire area to react with the formation of one large hive covering the entire surface exposed.

doses of morphine. It is not exceeded in its severity by the headache of brain tumor, acute sinus infection or migraine. It is practically always a general symptom and for this reason is usually associated with reaction in other localities.

In one patient it was associated with an outpouring of watery nasal secretion and itching about the neck and profuse secretion of sweat from the scalp. After several attacks which could be cut short by adrenalin, these symptoms disappeared and were followed by chronic asthma.

Headache of this sort is prone to accompany the reactions which immediately follow the use of salvarsan, pollen extracts, or blood transfusion. It is often associated with pain in the lower spine which evidently has the same pathogenesis and which may be equally severe. Recovery has been complete in every case which I have observed.

Headache of this source can easily be mistaken for migraine or headache of other sources. It can usually be differentiated, however, by the history and other manifestations so characteristic of allergic reactions.

## Neurologic Symptoms

**Asthenia** is a rather common manifestation of general reaction. It may vary from a slight feeling of weakness to asthenia so profound as to prevent the patient from lifting a hand. I have never observed a patient more profoundly asthenic than one whom I saw in consultation a few years ago who had been given a therapeutic dose of diphtheria antitoxin. The patient was undoubtedly a horse asthma case. Within a few minutes after the injection, she had a rigor followed by weakness of such grade that she could scarcely talk, could not turn over in bed, or raise her hand above her body. This symptom in less severe grade is relatively common in patients with mild general allergy and is frequently felt after the therapeutic use of pollen extracts. It is rarely observed in contact reactions, such as pollen hay fever, unless the patient is excessively sensitive or unless exposure has been severe and prolonged.

**Convulsions, Paralysis, Paresthesia, and Anesthesia** are rare but definite complications of allergy.

CASE 12.—*Migratory Paralysis and Anesthesia Associated with and Alternating with Asthma.*—Paralysis and anesthesia in the one case I have had the opportunity of studying was migratory and transitory. This patient, a woman of forty-five, for one year had been subject to convulsions associated with involuntary discharge of urine and feces followed by coma occurring once or twice daily. Many of the convulsions were followed by temporary paralysis or anesthesia of one of the extremities. Coma would sometimes last a number of hours and paralysis or anesthesia several hours additional. The attacks occurred at irregular times, even during sleep, and occurred even when the patient was taking large doses of bromide or luminal. The attacks had a tendency to alternate with asthma but both symptoms occasionally occurred together.

Upon administration of epinephrin, she would promptly recover and when

epinephrin was given at regular intervals, she enjoyed complete freedom from both neurologic and bronchial attacks.

Upon testing, she was found hypersensitive to several fruits and vegetables and upon omitting these from the diet, she could be kept relatively free of attacks if epinephrin was occasionally administered. During a well period, attacks could be brought on by the eating of vegetables to which she had given positive skin tests.

It seemed, without question, that these attacks were traceable to an involvement of some of the cerebral tissues by the same process which caused her to have asthma.

**Mental Disturbance** in patients with chronic allergy is observed with relative frequency. It resembles delirium and bewilderment rather than a psychosis. Any illness, the manifestations of which are so profound as those of severe allergy, could be expected to interfere with cerebration in considerable degree. It is not unlikely that cerebral edema (the existence of which we might surmise) is primarily responsible for mental disturbance in some cases.

### Dizziness and Ménière's Syndrome

Dizziness rather frequently accompanies other general manifestations of allergy—in fact, allergy seems to be a relatively common cause of dizziness.

In two cases observed by the writer, the patients were subject to attacks of dizziness associated with tinnitus, nausea, and vomiting which would cause them to fall helpless to the ground. The slightest movement made by themselves or others during one of these attacks would make the symptom much more severe and would initiate, usually, an attack of vomiting. Each patient was afraid to venture out of the house for fear of injury.

Case 13.—*Ménière's Syndrome Caused by Foods.*—An unmarried woman, aged thirty-five, came to me complaining of attacks of dizziness, nausea, and fainting. The family history was negative for allergy so far as she knew. Her past history was uninteresting, except for the fact that she had been subject to hives during the summer months for the past fifteen years.

The present illness started several years ago with slight dizziness, which she noticed off and on in slight degree since. Several weeks before coming to me, she began to have more frequent attacks of dizziness associated with tinnitus and nausea. In the more severe attacks she would fall to the floor and be unable to walk. During this period she would feel as if she were rolling over and over. After a period of from one-half hour to three hours she would recover and feel relatively well except for slight dizziness, which would persist. Severe attacks such as these would appear once every day or two.

*Physical Examination,* including the nose, ears, throat, chest, abdomen and pelvis, showed nothing abnormal except tenderness with slight muscle spasm on pressure over the appendix. This was noticed on several examinations, and a diagnosis of chronic appendicitis seemed justified.

*Laboratory Examinations,* including Wassermann tests with cholesterinized antigen and one unit of complement, were negative.

*Roentgen Ray Examinations,* including the nasal sinuses, mastoids, and gastro-intestinal tract, were negative. Roentgenograms of the teeth showed one small granuloma.

*Functional Tests of the Ear,* including Barany's, made by Dr. Sam E. Roberts, were negative except as follows: The vestibular tracts were all open, but responses both for nystagmus and past pointing were subnormal. Cochlear tests showed a reduction of about one-fifth for bone conduction and for high tones.

*Intracutaneous Tests,* with many of the fruits and vegetables gave very marked delayed reactions. The most marked tests were obtained with peas and beans. Intracutaneous group tests with extracts of all the common meats, fish, fowl, eggs, dairy products, nuts, condiments, grains, pollen, animal hair, and feathers were negative. The tests were followed after several hours by a very severe attack of Ménière's syndrome.

The patient, during an attack, was given 1 c.c. of epinephrin subcutaneously, with marked immediate improvement in the symptoms. She was given 0.75 c.c. of epinephrin subcutaneously each morning and evening for two weeks thereafter, with the result that she had no more severe attacks and fewer mild attacks. She was put on a diet free of fruits and vegetables for a period of two weeks, and epinephrin was omitted. The result was a period of almost complete freedom from symptoms except very slight dizziness occasionally.

She was then allowed to eat the vegetables to which she had given positive skin tests. After six hours a very severe attack of dizziness, associated with hives, recurred.

A diet almost free of protein, but containing a few vegetables, gave no relief whatever; in fact, it was discontinued at the patient's request after two days.

CASE 14.—*Ménière's Syndrome Caused by Food.*—A man, aged forty-three, came to me complaining of seasonal hay fever and asthma, and attacks of dizziness and vomiting. His father was subject to hay fever. A brother was subject to seasonal hay fever and asthma. A sister was subject to perennial asthma. The past history was negative except for earache in childhood. The patient had been subject to autumnal hay fever for about twenty years. For the last fifteen years this had been associated with severe autumnal asthma, which at times confined him to bed for several weeks at a time unless he left this climate. For five years he had been subject to attacks (Ménière's syndrome) which would start by profuse sweating, followed after about one minute by roaring in the left ear, followed in about three minutes by dizziness and vomiting. Objects would seem to whirl around during this period. The patient was made worse by the least movement of the head. During these spells he was forced to keep absolutely motionless for periods of from one-half hour to four hours, when the attacks would gradually subside. Very slight dizziness would persist for almost

one week after the attack, after which he would be relatively well for a time. The attacks occurred regardless of time of the year, time of the day or night, and regardless of geographic locality. In all, he had about fifty severe attacks, and during the past several months he had slight dizziness and uncertainty in his feelings almost constantly.

The severe attacks bore no marked relationship apparently to the seasonal hay fever and asthma. On careful questioning and careful observation for one month, it was found that he could bring on severe attacks by the eating of spinach, vinegar and certain fruits, especially prunes. He remembered then that his most prolonged and severe attacks occurred when eating prunes for the relief of constipation.

*Physical Examination* was negative except for deviation of the nasal septum to the right and partial deafness, with increased bone conduction in the right ear. Other examinations, including the eyes, throat, abdomen, and prostate, were negative or of no interest in this connection.

*Laboratory Examinations,* including Wassermann tests with cholesterinized antigen and one unit of complement, were negative.

*Roentgen Ray Examinations,* including the nasal sinuses, mastoids, teeth, chest, and gastrointestinal tract, were negative.

*Functional Tests of the Ear,* including Barany's, made by Dr. Roberts, were negative except for reduced hearing with increased bone conduction on the right side and subnormal responses for nystagmus and past pointing. The vestibular tracts were all open.

*Intracutaneous Tests* made with all the common foods and air-borne allergens showed the following: Group tests with the common vegetables, fruits and nuts, gave very strong positive reactions. Most marked was the reaction obtained with an extract from spinach; tests with the common air-borne allergens were positive for some of the furs, dusts, and spring and fall pollens; positive ophthalmic tests were obtained only with the pollen or marsh elder, Spanish needle, pigweed, and small ragweed; intracutaneous tests and ophthalmic tests made with other air-borne allergens were negative. Intracutaneous group tests made with extracts of all the commonly eaten meats, fish, fowl, eggs, dairy products, grains, and with bacterial extracts gave negative or only slightly positive reactions.

On two different occasions the patient had a severe attack of dizziness and nausea, which started about six hours after the use of intracutaneous tests with extracts to which he reacted positively. The attacks lasted about twelve hours, and were then markedly relieved by epinephrin. This result was later obtained with the use of spinach extract alone.

At an earlier date, severe spontaneous attacks were also relieved within fifteen minutes by the subcutaneous injection of 1 c.c. of epinephrin (1:1000 solution). The asthmatic attacks were likewise relieved by epinephrin, but a little more time was required.

The patient was put on a diet free of all fruits, vegetables, and nuts; that is, on a meat, dairy, egg, and wheat diet. During a period of thirty days he was practically free of attacks, although he felt slight dizziness at times. He was steadier on his feet at all times, however, and noticed a very marked

reduction in tinnitus and in the subjective feelings, which formerly were very disagreeable and were often followed by the symptoms described as Ménière's syndrome.

At the end of one month he ate spinach with vinegar as a test. It was followed within six hours by dizziness, which required epinephrin for relief.

At the end of this study, the pollen season began and during the season and during the pollen treatment that was given he was subject to attacks of asthma and one slight attack of Ménière's syndrome even when on a diet free from vegetables and fruit. The attack was believed due to a treatment with pollen extract which he had received.

### Urologic Manifestations (Renal Colic—Irritable Bladder)

The symptoms, frequent urination and bladder tenesmus, are rather frequently the result, I believe, of general allergy, especially in the case of hypersensitiveness to foods. I have observed it in patients following the ingestion of fruits, vegetables, sea foods, and cereals. The condition may vary in severity from slight discomfort to pain and tenesmus which confines the patient to bed for months. Bladder allergy of long standing may be complicated by infection in which case the symptoms of cystitis obscure the diagnosis. In one case it was complicated by polyps which surrounded the internal urethral meatus. This was thought to be a result of chronic edema of the mucous membrane.

In patients having chronic bladder allergy, frequently no pathology can be found by internists, urologists, neurologists, roentgenologists, or pathologists except hypersensitiveness to foods. Frequently the case may be misdiagnosed as cystitis, urethral caruncle, misplaced uterus, or pelvic inflammatory disease. Treatment of such conditions often give partial relief, but as a rule, the bladder symptoms continue as severely as before. This type of case is encountered rather frequently in the practice of medicine, especially in women, and the most careful and diligent examination may not disclose evidence which makes a rational diagnosis possible unless food tests are made.

Case 15.—*Irritable Bladder Caused by Foods.*—A woman, aged twenty-two, was referred by Dr. M. T. Dingess, because of "bladder trouble."

The family history was negative for allergy so far as she knew.

The past history was important only for the fact that she had been subject to urticaria at odd times in her life.

For two years before coming to me, she was troubled with frequent burning urination which was at times so severe as to confine her to bed. She had been

treated under many different plans without relief—in fact, she had not been free from bladder pain for a single day during her illness of two years. She was treated under my advice for ten days with bladder sedatives without relief.

*Physical Examination* showed poor nutrition, chronic pelvic inflammatory disease, cervical tear, tenderness over the bladder both by abdominal and vaginal examination, tenderness in both kidney regions, and marked evidence of ptosis.

Catheter specimen of urine showed nothing of interest except an occasional pus cell and low specific gravity.

Other laboratory examinations, including Wassermann reactions, were negative.

*X-ray Examinations* disclosed no stone and nothing of further interest except ptosis.

Examination of the bladder and urethra by Dr. J. E. Burns showed nothing abdominal.

*Sensitization Tests* showed marked sensitiveness to wheat and slight sensitiveness to several grains (barley, rice, and oats). The reaction to wheat appeared a moment after intracutaneous injection of 0.01 mg. of wheat protein extract, reached maximum size after several hours, and did not subside until the following day. All tests were followed after about ten hours by an unusually severe attack of frequent, painful urination which lasted for twenty-four hours. She was given adrenalin to relieve this attack. She was then told to avoid all grains, especially wheat and its derivatives. All other medication was discontinued. Two days after this she was completely free from bladder disturbance for the first time in two years.

She has continued well now for six weeks after discontinuing wheat, except for two attacks of one day each which followed about twelve hours after the eating of wheat flour as a test.

CASE 16.—*Irritable Bladder Caused by Foods.*—Woman, aged twenty-three, came to me complaining of urticaria, hives, and puffiness of the eyes.

The family history was negative so far as the patient knew except that a grandparent had asthma.

She gave a history of occasional attacks of hives since scarlet fever at the age of eleven, which attacks would rarely last more than one or two weeks. With these seizures she frequently experienced burning, painful urination. Often bladder symptoms preceded the urticarial outbreak and continued for several days after it had subsided. At times, during the bladder attacks, the patient voided involuntarily.

With the seizures just described, the patient frequently had nausea, vomiting, sour stomach, and eructations, accompanied by slight pain in the epigastrium, not modified by foods. She had occasionally noticed mucus in the stools.

History was otherwise of no interest in this connection.

*Physical Examination* disclosed nothing of interest except urticaria, angioneurotic edema of the eyelids, and edema of the conjunctivae.

The urine was pale with a specific gravity of 1.008 and contained an occasional pus cell.

Examination of the stomach juice showed an achylia. Other laboratory examinations, including Wassermann reactions, were negative.

*Cystoscopic Examination,* made by Dr. J. Edward Burns, was negative.

*Intradermal Tests* showed marked sensitiveness to milk and to several grains, most marked to oatmeal. The wheals appeared almost immediately after the intracutaneous injections, but reached a maximum only after several hours. They did not disappear for more than thirty-six hours.

Following the injection of 0.01 mg. of material extracted from oatmeal, which was made on two occasions, the patient had a severe attack of frequent, very painful urination; this began about six hours after the inoculations were made and lasted four days. During these attacks she also had asthma for the first time in her life.

After discontinuing the foods to which she was sensitive (oatmeal and milk) her symptoms disappeared quickly and completely. The patient has noticed since this time that she can bring on hives and bladder pain invariably by drinking milk or by eating oatmeal. She is, at other times, free of both the cutaneous and bladder symptoms of which she complained.

CASE 17.—*"Renal Colic" Caused by Foods.*—The patient, a woman of thirty-four, came to me complaining of attacks of pain in the left flank which were so severe as to lead her husband, a physician, to take her to many surgeons and specialists—in fact, among them were six of the best-known surgeons and urologists in the United States.

Her attacks began about nine years ago, occurring in the beginning at about two or three week intervals. They would last for one-half hour or more, when $\frac{3}{8}$ to $\frac{1}{2}$ gr. of morphine had to be given for relief. The attacks became more frequent, finally occurring at two-day intervals. There were occasional remissions, lasting a week or more but never one lasting longer than one month.

The pain would start gradually in the left flank, increase in intensity until it became almost unbearable, and would then radiate toward the left costovertebral angle and down the inner side of the left thigh and occasionally to the left heel.

Many of the attacks were associated with frequent painful urination, and bladder tenesmus and frequently with an outbreak of purpuric spots which occasionally would cover almost the entire body. Some of the attacks were followed by an outbreak of itching hives. The urological history and past history was otherwise of no interest except for the fact that she was very sensitive to quinine, and had dysmenorrhea at two to three week intervals.

The family history was interesting in that her grandfather had asthma, a sister is sensitive to quinine, and a nephew had severe asthma.

*Physical examination* was negative except for low blood pressure (104), slight tenderness in the left flank, and urticarial dermographia.

*Laboratory examinations* were negative throughout.

*X-ray examinations* negative except for the finding of one devitalized tooth.

Sensitization tests negative except for small delayed reactions following the intracutaneous injection of some of the extracts of the meats, vegetables, fruits, and grains.

Sensitization tests made by the application of physical agents, such as heat and cold in various localities, were negative except for wheals which followed mechanical irritation of the skin.

At the time of the examination, the patient was having attacks of pain at two-day intervals which required morphine. During an attack, she was given one-half c.c. of adrenalin with almost immediate relief. This has been repeatedly tried since, always with the same result. Morphine did not give relief within a period of less than twenty minutes. Morphine, atropine, and aspirin, which had been repeatedly required during a period of nine years, were discontinued and have not been used once during the three subsequent months.

Since skin tests with food extracts gave unsatisfactory results, she was tested with foods by mouth. One after another group of foods were avoided for intervals of one week. No result was obtained until she was put on a purine-poor diet—that is, a diet in which meat, fish, chicken, soups, gravy, tea, coffee, chocolate, peas, and beans were carefully avoided. On this diet, she did not have a single attack. She then tried to add the following purine-containing foods to the diet; namely beef, ham, bacon, oysters, tea, coffee, chocolate, cocoa, peas, and beans. Each test was followed within two and one-half hours with a typical attack of severe pain in the flank which was relieved immediately by the use of adrenalin. Unbelievably small amounts of the foods mentioned would cause an attack.

As previously mentioned, this patient had been examined clinically, urologically, and otherwise by many eminent physicians and specialists and none found what seemed to them to be a definite adequate cause for her complaint and no definite diagnosis was suggested except for the possibility of ureteral stricture and ureteral spasm. Every sort of examination was made including pyelograms and functional tests, all with negative or doubtful results. None of the agents used for relief were effective except morphine and to a smaller extent, atropine and aspirin.

On the diet mentioned, the patient has not only been free of attacks of pain, but her menstruation has become regular and free from pain. She has gained ten pounds in weight and discontinued the use of narcotics.

## Disturbance in Menstruation

Disturbances in menstruation are rather frequently observed in patients having symptoms as a result of general reaction. Cooke mentions a case in which dysmenorrhea occurred as a result of a treatment with foreign substance. A wide variety of symptoms have been observed in my cases which have disappeared after appropriate treatment. In one food sensitive case, menstruation which had not only been extremely painful but which had occurred twice monthly for years, became completely normal and occurred at four-week intervals upon avoidance of the foods to which she reacted.

## Arthritis

Joint pain and swelling is a very definite and interesting manifestation of allergy. It is frequently observed in patients with

serum sickness. My friend, Dr. R. C. Lowdermilk, in 1912, related to me the case of a patient who, following a therapeutic injection of pollen, developed a typical rheumatic joint, for the first time in her life; it lasted several hours during her reaction, and then disappeared completely. There is some similarity between the joint symptoms of acute articular rheumatism and that of a reaction of allergy. For example, the pain and swelling may migrate from joint to joint within a period of a few hours, or in fact, at times, almost within a period of minutes. It is impossible that symptoms due directly and entirely to local infection, could appear or disappear at such a rate. Migration and rapid change, on the other hand, is one of the striking characteristics of symptoms due to allergy. While there is no doubt that acute articular rheumatism (i.e., acute migratory polyarthritis) is an acute infectious disease, it is not impossible that some of the local symptoms, such as pain and swelling, is in part the result of an allergic reaction about the infected joints, in fact, I have used adrenalin in the treatment of acute articular rheumatism in several cases with brilliant temporary results and believe it is a useful aid to removal of cause and salicylates in the treatment of this disease. Adrenalin in hypertrophic, atrophic, and chronic infectious arthritis yields less but often some temporary beneficial effect.

Arthritis occasionally accompanies other general manifestations of reaction although it is uncommon.

### Hypotension

Allergy is perhaps the commonest single cause of hypotension. Since allergy afflicts probably as many as 10 to 15 per cent of individuals and since a blood pressure of from 90 to 110 is the rule during attacks, it can be readily understood that as a cause of hypotension, tuberculosis ranks second, perhaps, to allergy. Whereas a reduction to 90 millimeters is common, a reduction to almost nothing is occasionally observed during severe reactions.

### Eosinophilia

Koessler states that a differential count showing eosinophils in excess of 5 per cent is abnormal and found an eosinophilia in excess of this quite constantly in hay fever cases. I have found the same in the great majority of cases (even physical cases) in which this examination was made during periods of reaction.

# CHAPTER XV

## SPECIFIC DIAGNOSIS

There exists in the minds of physicians generally a gross error concerning the value of skin tests in the specific diagnosis of reaction, and concerning the conclusions which can be drawn from them. Skin testing and materials prepared for skin testing have been so exploited that the profession at large has conceived the idea that from skin tests alone the average case can be correctly diagnosed. No idea could be more false than this.

Most physicians who become interested in this branch of work quickly become discouraged with the result of skin tests. They usually buy materials first from one commercial house and then from another, and finally consult their friends about their experience, asking, usually, where reliable materials can be obtained. The fact is that the fault cannot be traced nearly so often to materials used for testing as it can to the fact that scarcely 25 per cent of chronic perennial cases can be correctly diagnosed through the use of skin tests of any sort. This percentage varies with the class of patients which happen to consult the physician. Patients sensitive to pollen, animal hair, and other air-borne substances usually give positive skin tests and through them, useful information can often be gained. In perennial cases and food cases, however, the result is usually disappointing. If one can gain information which is useful in as many as 50 per cent of cases of all types through the use of skin tests, he should consider himself unusually fortunate.

In this chapter, I wish to deal particularly with the diagnosis of reaction in patients who are sensitive to, and react to, material agents—that is, to material agents as contrasted with physical agents, to be discussed in Part II. Several sources of information are useful in specific diagnosis—in fact, almost essential. From them, one can very frequently discover not only whether or not a given illness is fundamentally allergic in origin, but also what the source and distribution of the agent primarily responsible for reaction may be. It is frequently difficult or impossible to discover

exactly what the specific agent is. This, however, is not all important if one knows its nature, locality, and distribution.

The following sources of information are useful:

Family history.

Personal history.

Physical, laboratory, and x-ray examinations.

Careful observations made by the patient.

The effect of adrenalin upon symptoms.

Specific tests (cutaneous, intracutaneous, ophthalmic, nasal, subcutaneous, and clinical).

Whereas these measures often give a clue concerning the source of an illness, a diagnosis can rarely be proved by any of them. Proof depends upon obtaining relief of symptoms by removal of the suspected cause, and finally, upon reproducing symptoms during a well period, by bringing the patient again in contact with the suspected substance in a more or less natural way. Surprising as it may seem, it is certainly true that even when these two fundamental requisites are complied with, an error in diagnosis is possible, though improbable. The reader can possibly be convinced of this by my citing again the case of tabes dorsalis in a patient in whom lightning pains were induced by the eating of apples and peaches and also a patient to be reported subsequently (urticaria calorica) who reacted to the effect of physical exercise. The source of the trouble was actually traced, not directly to the effect of exercise, but to the small amount of heat generated by exercise. A typical reaction could be produced in this patient by heat of any source, and could be prevented by the application of cold of any source. Even here, we are not necessarily dealing with primary causes, because such patients may actually be sensitive to some new substance generated in the body or in a nerve center under the influence of heat. I am admittedly degressing some from my subject in discussing physical reactions at this point, but I know of no case which illustrates so well the many difficulties encountered in tracing out primary causes in this type of illness.

The following two histories given to me by Dr. M. F. Meixner of Peoria, Ill., serve to illustrate the value of histories and careful observation in the diagnosis of a case. They exemplify practical logical methods of study.

CASE 18.—*Asthma Caused by Material on the outside of Egg Shells.*—The patient, a woman of thirty-two, gave a negative family and personal history so far as hay fever, asthma, and hives were concerned. She consulted her physician because of asthma which had recurred each morning for three weeks, lasting about three hours. At other times during the day she was normal.

*Physical examination, laboratory examinations,* and roentgen examinations were all negative.

Sensitization tests were negative.

Careful questioning showed that the attacks occurred soon after she cooked breakfast. She was asked to avoid the kitchen for several days, during which time she was free of asthma. On the fifth morning, when she again prepared breakfast, she had an attack. She was then allowed to be in the kitchen while her mother prepared breakfast, being careful, however, not to touch food or anything about the stove. She was free of asthma on this day. She was then allowed to cook a meal with gloves on and had no asthma. After the meal was over, the gloves were turned inside out and worn for one half hour with the result that she had a very severe attack which lasted longer than usual. Dr. Meixner concluded from this that she was sensitive to one of the foods which she had cooked and handled. She was allowed to handle several of the foods which were ordinarily used for breakfast. She had asthma only after she handled raw eggs. During a well period, she was allowed to hold an egg in her bare hand. A severe attack of asthma followed. She was then tested cutaneously with the commercial egg shell extract and with egg protein with negative results. She was then tested with an aqueous extract from shells of eggs laid by her own hens. A typical wheal followed this test. The cloacal secretion of several of the hens was obtained and used as a test, but gave negative results. When the patient was allowed to go into the hen house and collect eggs without gloves, she developed asthma but with gloves she did not. The patient was then told to buy eggs at the grocer and try them. She gave no reaction upon cooking them. She was allowed to handle hen's nests, chicken feathers, and other things about the place, also eggs layed by her own hens which had been washed, all with negative results. She was told to dispose of her chickens, and since then has been free of asthma. Dr. Meixner concluded that this was an example of sensitiveness to a material on the outside of egg shells in which the reaction was specific for eggs laid by certain hens or laid under certain conditions peculiar to her environment.

NOTE: While this case may sound fantastic to the reader, it is not out of line with observations of sensitiveness to other agents, such as strawberries or cantaloupe specific for those grown in certain limited localities or to pollen produced in certain limited localities.

CASE 19.—*Asthma Caused by Sensitiveness to Salted Roasted Peanuts.*—The patient, a girl of six and one-half years, with negative family and personal history, for some six months developed asthma accompanied by marked cyanosis and copious bronchial secretion whenever she went down town. Upon two occasions she was brought home in an ambulance because of the severity of the attack.

Physical examination and laboratory tests between attacks were normal. Examination during an attack showed musical râles in the chest, tachycardia, cyanosis, and marked depression.

Upon watching the child in an endeavor to obtain a clue as to the cause of the illness, it was observed upon one occasion that they occurred after the purchase of a sack of peanuts. The mother was then instructed not to allow the child to have peanuts for one week. During this week, she had no attacks. The child was then given one-half peanut by mouth. A mild but typical reaction followed. The nut, inner husk, and shell of an unroasted peanut was then extracted and used for cutaneous testing. Negative results were obtained. A salted roasted peanut was then extracted and upon using it as a test, a typical wheal was obtained. Salt alone did not produce the reaction. Neither did an extract of a roasted, unsalted peanut.

She was treated by having her avoid salted roasted peanuts with a perfect therapeutic result. She was then given gradually increasing doses of powdered roasted salted peanuts by mouth with a gradual increase in tolerance.

NOTE.—I wish to express my thanks to Dr. F. M. Meixner for his courtesy in allowing me to use these very carefully studied cases which exemplify, not only the high degree of specificity in sensitiveness to foreign matter, but the patience and care necessary for the unraveling of an obscure case. It is work of this type which enables one to correctly diagnose a large percentage of cases.

### Family History

Specific hypersensitiveness is one of the most consistently hereditary of diseases. In outspoken cases, a positive history of the condition in one or both parents can be elicited in almost 50 per cent of cases. Cooke and Vander Veer, and later Adkinson, each report an antecedent history in nearly 50 per cent of cases studied. Each also found that, with a positive history in both parents, the disease appeared at an earlier age than when it was obtained in one parent only. A positive family history, therefore, is very important confirmative evidence in diagnosis.

### Personal History

A number of symptoms are characteristic of hypersensitiveness. Worthy of special mention are the ocular (edema of the conjunctivae; puffiness, redness, swelling and itching of the lids; and increased lacrimal secretion); the nasal (sneezing, pallor and swelling of the mucous membrane of the nose, associated with watery or clear mucous secretion); the pharyngeal (itching of the soft palate and pharynx, and cough); the bronchial (bronchial obstruction associated often with wheezing and the expectoration of clear

mucoid sputum rich in eosinophils—in lighter cases, cough and shortness of breath on exertion), and the cutaneous (urticaria, angioneurotic edema, eczema, erythema and pruritus). Much less characteristic are the gastrointestinal symptoms (abdominal pain, often following the ingestion of certain foods, and gastrointestinal upset presenting a variety of symptoms); the bladder symptoms (frequent painful urination), and headache, nervousness, asthenia, hypotension, and the like. The foregoing symptoms always suggest the possibility of reaction, especially when they occur in the absence of other apparent adequate cause for an illness, and when the family history is positive.

### Physical Examination

The more important signs of allergy which can be found on physical examination are the ocular, the nasal, the bronchial and the cutaneous. Cutaneous symptoms can occasionally be brought out by scratching the skin. This occasionally gives rise to the immediate appearance of typical wheals. Examination is also important in excluding sources other than reaction for a given complaint. For example, if, in a patient with a long history of frequent and painful urination, physical, cystoscopic, endoscopic and Roentgen ray examination, and urinalysis reveals nothing abnormal, bladder allergy must always be suspected, especially if the patient gives a history of hives, asthma, or other characteristic symptoms of the condition, and if a history of such symptoms in the parents can be obtained.

### Observations by the Patient

Practical observation by both physician and patient is important. It is often advisable, in an obscure case, to school the patient thoroughly in the mechanism of hypersensitiveness so that his observations may be directed along useful channels. He should observe whether or not the origin or relief of symptoms bears any relationship to season, time of day, geographic situation, local environment, the proximity of animals or fowl, the eating of a food, the use of cosmetics, wearing apparel, odors, habits, etc. Important information can often be gained through careful observation by the patient, which makes a correct diagnosis possible.

CASE 20.—*Asthma Caused by a Rug.*—I may mention the history of a woman who was subject to asthma while in her own house but was relatively free of asthma in other localities. She gave a positive skin reaction to an extract of dust taken from her vacuum cleaner. She remembered, then, that her asthma, of four years' duration, dated from the purchase of new furnishings for her house, among which was a large rug. The rug was thoroughly cleaned with a vacuum cleaner, and saline solution was allowed to filter through it several times. The solution was then filtered through a stone filter, and injected intracutaneously. A marked local reaction and an attack of asthma immediately followed. Disposal of the rug resulted in immediate relief. The patient was not sensitive to wool or to other extracts of animal hair, or to extracts similarly made from other articles about her house.

Symptoms which appear only in the spring, summer, or fall, or bear a relationship to geographic situation are usually traceable to plant life (usually to pollen, occasionally to emanations from the bloom, leaves, or stalk). Symptoms which bear a relationship to local environment, such as house or work shop, are often traceable to dust, insect powder, cleaning fluids, smoke, or some article or animal in the house. Among dentists, eczema or asthma is frequently traceable to sensitiveness to cocaine, novocaine, or apothesine. An undertaker whom I examined was sensitive to formaldehyde; a patient, subject to chronic asthma, worse in her own house than elsewhere, had a severe attack after the painting of her house and was proved sensitive to turpentine; another, subject for several years to nasal reaction, proved to be sensitive to orris root. She was relieved after discarding cosmetics, and especially after disposing of a sachet which she kept in her dresser drawer. Even wearing apparel taken from the drawer caused attacks.

Occasionally, it seems impossible to discover the specific agent responsible for house allergy. One of our patients, an undertaker, had to give up his business on this account. He was able to work without ill effect in other establishments of the sort in which apparently the same embalming materials were used.

Symptoms which bear a relationship to stables are often traceable to an animal, occasionally to emanations from vegetable matter, such as hay. Symptoms which bear a relationship to city or railroad cars are often traceable to smoke; to farms and country, often to plant life; to time of day, often to an article with which habit brings the patient into contact. Night asthma is occasionally due to house dust, wool, or feathers. Night attacks, however, seem to

be more often a result of temperature sensitiveness to be described in Part II.

Symptoms which follow the eating of certain meals are often traceable to an article of food; if the symptoms appear frequently, to a common article of food, and if rarely, it is an unusual article of diet.

Often the working out of an obscure case depends as much on detective work as on the persistence of the physician, and success can occasionally be attained only by visiting the patient's home or shop, and making careful observations.

## Specific Clinical Tests

Useful crude clinical tests can often be made by having a patient eat a suspected food, or inhale a suspected vapor or the odor of suspected perfume, or the emanations from fur, feathers, animals, etc., or by the application of suspected substances to the skin. Such tests often make a correct diagnosis possible in the simplest sort of way and are also very dependable when positive results are obtained. Frequently, however, this method of testing presents difficulties. In a person who is sensitive to several articles of food, such as milk, eggs, and certain vegetables, the greatest persistence in eating or in avoiding certain foods may fail utterly to give the diagnosis. This is especially true when reactions are delayed. In one patient with asthma who had been treated by several careful physicians, the primary source of the disorder (which proved to be both milk and egg) were missed entirely by clinical tests because of the fact that the patient gave delayed reactions in each case and was sensitive to two common articles of diet. After the offending agents were suspected through the use of skin tests, the patient was able to obtain complete relief by the simultaneous avoidance of both milk and egg. The diagnosis was then proved by the fact that thereafter typical attacks of asthma would follow ingestion of a small amount of either milk or egg. The symptoms never appeared sooner, however, than thirty-six hours after the injection or the ingestion of the offending substances.

## Skin Tests

Two methods of making skin tests are used at the present time, the cutaneous, or scratch method, advocated particularly by

Fig. 61.—Positive cutaneous and intracutaneous tests made by applying honey to a scarified area on the skin (above) and by injecting a dilute solution intracutaneously (below). It exemplifies the fact that in some patients both tests give the same result. This is usually the case with patients who give immediate reactions at the site of contact with substances to which they are sensitive.

Fig. 62.—Positive intracutaneous delayed reaction (above) and negative scratch test (below), obtained by treatment of the skin with the same agent, lactalbumin. This is not an uncommon finding in cases in which general reactions rather than reactions of surface contact follow exposure to a substance to which the patient is sensitive. The value of reactions of this type in diagnosis is much smaller than that of reactions such as those shown in Fig. 61.

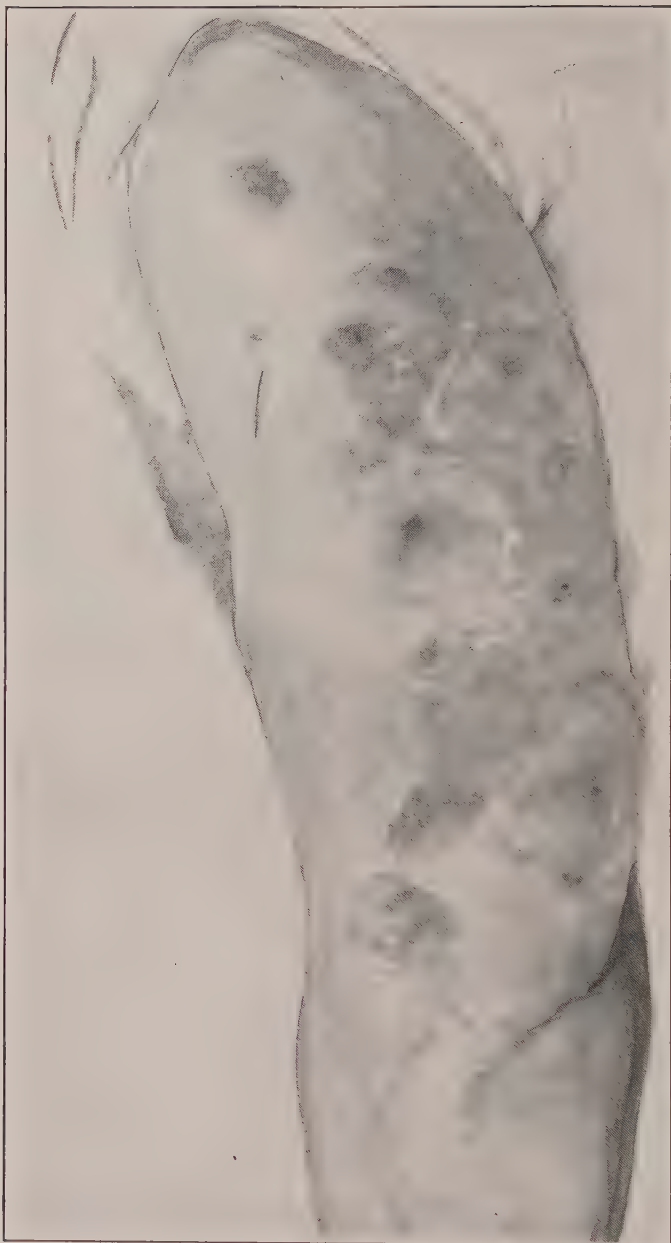

Fig. 63.—Large delayed reactions which appeared about thirty minutes after the intracutaneous injection of food extracts in a patient with angioneurotic edema. These reactions reached a maximum intensity only after a period of several hours and lasted several days. This is not an uncommon finding in food cases subject to delayed general reaction. This type of sensitiveness varies from time to time. See Fig. 64.

Fig. 64.—Negative intracutaneous tests obtained in the case illustrated in Fig. 63 after a period of three months. The patient at this time was not sensitive clinically to any of the foods which had previously caused illness and had given positive delayed reactions. Variability such as this is rarely observed in contact cases which give immediate hive reactions such as those shown in Fig. 61.

Walker, and the intracutaneous, advocated by Cooke and others. Both have a sphere of usefulness. The intracutaneous, the more delicate method, gives a greater number of positive reactions than the cutaneous, but has the disadvantage of giving a greater number

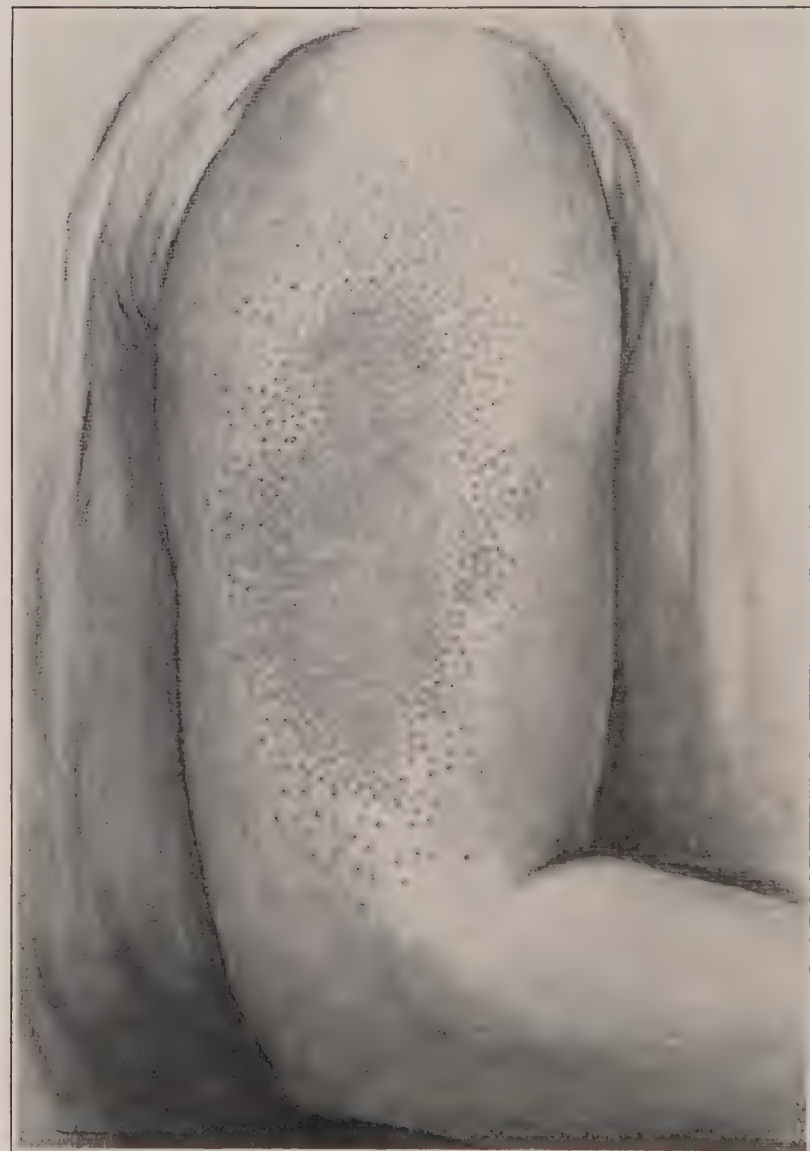

Fig. 65.—Illustration of a widespread eczematous reaction which appeared twenty-four hours after the application of the bloom of a ragweed to a small skin area on the arm. This reaction persisted for about ten days. Each small area is believed to have occupied the site of a pollen granule. The original small red areas coalesced after several days to form a large scaling, weeping, eczematous surface.

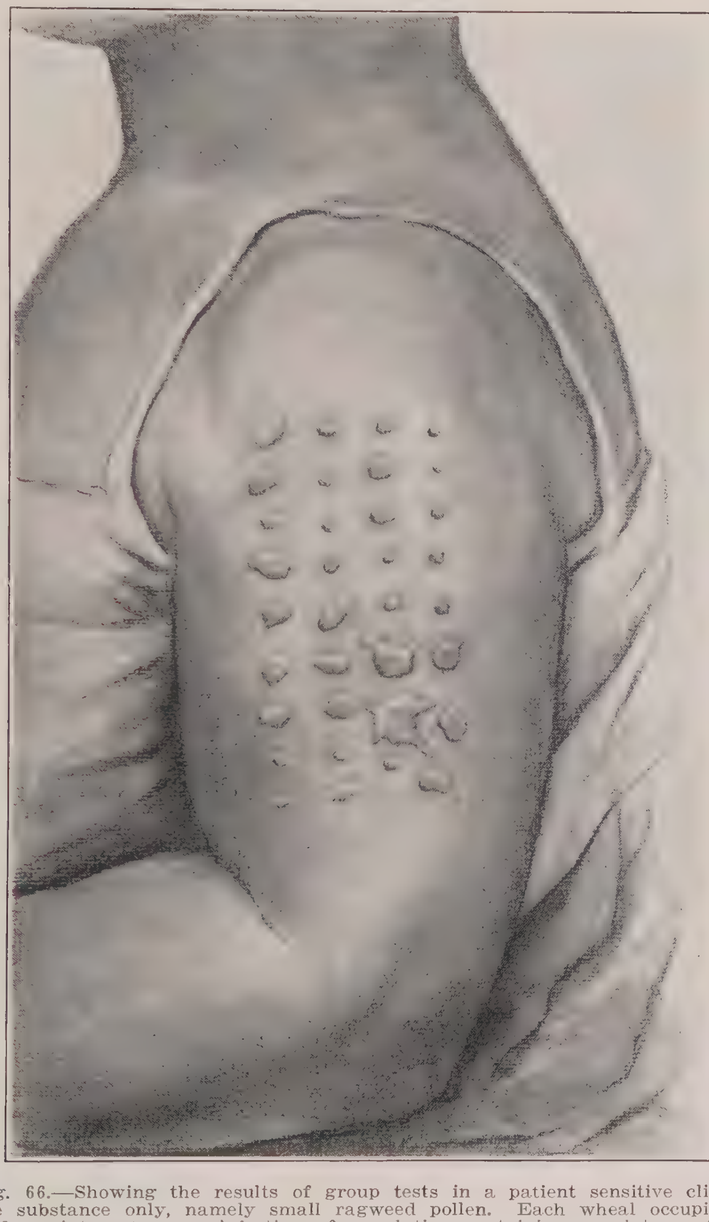

Fig. 66.—Showing the results of group tests in a patient sensitive clinically to one substance only, namely small ragweed pollen. Each wheal occupied the site of an intracutaneous injection of a solution containing a mixture of from five to ten extracts as illustrated in Chart II.

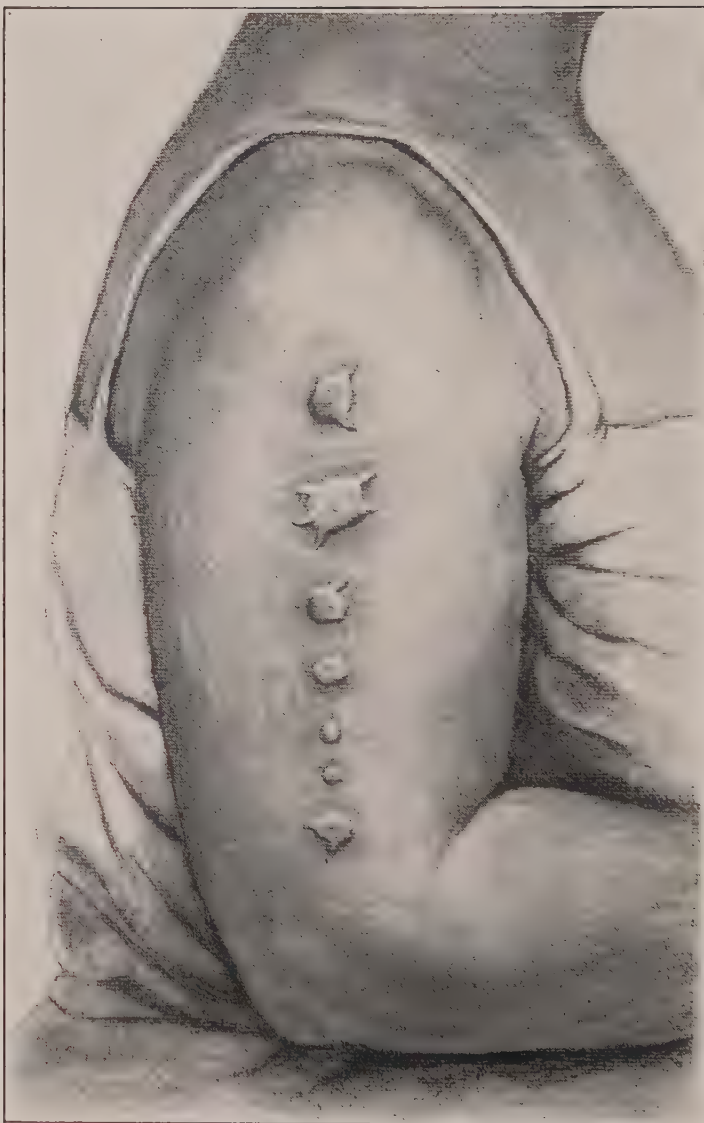

Fig. 67.—Shows the result of the intracutaneous injection of each individual extract contained in the mixture which gave the strongest test shown in Fig. 66. Skin tests even as strong and definite as these should be used as a clue only and not as a direct means of arriving at a positive diagnosis.

Fig. 68.—One Syringe Method: If a syringe used for making intracutaneous tests is washed thoroughly in three vessels of sterile salt solution, it can be used for subsequent tests. Such extract as might remain in the syringe is so diluted by the three washings that it does not interfere with the accuracy of subsequent inoculations. This makes it possible to use one syringe instead of a number and simplifies testing a great deal.

Fig. 69.—Rubber stoppered phials containing extracts for skin testing. The many solutions can be handled easily if put up in this way.

of false positive reactions, or, rather, giving a greater number of positive reactions in patients who are not clinically sensitive. This is no handicap, if the results are taken for what they are worth and what they actually indicate, and are used only in conjunction with information gained by history, physical examination and special tests. In this case, they are useful, and need not lead to serious error. The cutaneous reactions (or scratch tests) have their greatest sphere of usefulness in the testing of children (who react better than adults), and of patients sensitive to pollen and other air-carried substances. Patients of these types respond readily, as a rule, to cutaneous tests. Scratch tests are useful also for testing patients sensitive to agents such as turpentine, benzol, and other substances which might prove irritating or harmful if injected intracutaneously. Cutaneous tests often fail utterly in elderly individuals and in patients whose symptoms occur as a result of a general reaction (as in food cases). In these, intracutaneous tests often give more marked and convincing reactions.

In my experience, both the cutaneous and the intracutaneous methods are useful, and neither should be used to the exclusion of the other.

## Methods of Making Skin Tests

Methods of making tests are described in some detail because, in this work, relatively simple and at the same time relatively accurate methods are almost essential if this sphere of knowledge is to be used broadly by the profession. However, it must be added that skin tests in the hands of physicians unacquainted with their interpretation usually lead them into gross error. For them, common sense clinical tests and history are much more dependable.

**Cutaneous or Scratch Tests.**—By Walker's cutaneous method, the foreign materials in dry powdered form are applied to scarified areas on the skin, and to this is added a drop of tenth normal sodium hydroxide solution. The appearance of a hive, with pseudopods surrounded by an irregular area of erythema, indicates a positive reaction. The tests can be made more deftly if the skin is scratched in a number of places with a dull knife (the epithelium should not be cut) and solutions (0.1 per cent to 1.0 per cent) applied to them. The appearance of hives with pseudopods indicates positive reactions. Button reactions (hives without pseudopods) are called negative.

**Intracutaneous Method.**—Cooke and his associates advocate the use of standardized solutions in varying strengths and inject intracutaneously 0.01 c.c. The appearance of a hive, with pseudopods and erythema, indicates a positive reaction. Small reactions without pseudopods are disregarded. This method, while technically difficult, is very useful, especially in patients whose skin does not respond readily to cutaneous tests. The difficulty in technic does not lie in the injection of the solutions but in the preparation of solutions for testing. It necessitates the making of stock solutions at yearly intervals or oftener, and the repeated making of serial dilutions, some several hundred in number.

I have favored the intracutaneous method in my work except in cases where an unusually high degree of sensitiveness is suspected and in tests with substances which are not suitable for injection. In this case, scratch, inhalation, or ingestion tests are better.

### Simple Plate Method*

This method is useful to physicians who make relatively few tests.

Place about 0.1 mg. of each of the suspected substances (in dry powdered form) to be used in the tests on a large sterile plate. One-tenth mg. of a powdered protein can be guessed at crudely as the amount of powder which can be taken up easily on the end centimeter of a sterile Peerless round wooden applicator. To each powder add 0.1 c.c. of physiologic sodium chloride solution (distilled water will not dissolve globulin). Stir the first solution to be used and draw up in a tuberculin syringe provided with a small needle. Then inject 0.01 c.c. of the solution intracutaneously. Wash the syringe carefully in each of three separate vessels containing sterile physiologic sodium chloride solution. The syringe can then be used for injecting solution No. 2, and so on, if the syringe is washed thoroughly, and if the vessels of salt solution are always used in the same rotation.

Fontaine has suggested the use of 0.1 mg. tablets instead of the powders as used above. This modification reduces the limit of error, and also is easier to carry out. For physicians who test out

*The following firms manufacture dependable products which can be used in skin testing. Solutions are to be preferred to dry powders when their potency can be depended upon. Unfortunately, solutions tend to deteriorate with age and for this reason are less to be relied upon than powders. Lederle Antitoxin Laboratories, H. K. Mulford and Company, Swan-Myers and Company, Parke, Davis and Company, Cutter Laboratories, Arlington Chemical Company.

a number of patients daily (from two to ten), the use of stock solutions is much easier and better.

The advantage of the plate method lies in the fact that extracts in the form of a powder keep potent indefinitely if dry (according to my experience, more than six years), while solutions tend to deteriorate rapidly unless kept at ice box temperature. For this reason, potent extracts in the form of powders can be dispensed by commercial houses and can be kept indefinitely, thus relieving the practitioner of the laborious process of repeatedly making his own solutions.

That this method can be criticized as being only relatively accurate is admitted. It is inaccurate, but no more so than cutaneous (or scratch) methods. Inaccuracy in the scratch method lies in the fact that the quantity of solution absorbed by the skin is an unknown and variable factor, as is also the strength of the solution formed after the mixing of a powder and a solution on the skin. However, testing either cutaneously or intracutaneously by any method is of necessity only relatively accurate because of the lack of a method by which solutions can be standardized. We usually have little knowledge of the concentration in test solutions of the substances to which our patients react. This is well illustrated by the following case.

CASE 21.—*Sensitiveness to an Impurity in Aspirin.*—In a physician, severe attacks of abdominal pain were thought to be allergic in origin and due to the occasional use of acetylsalicylic acid. On account of the physician's statement that he often took acetylsalicylic acid without ill effect, he was tested intracutaneously with five different brands. He gave negative reactions with four and an intensely positive reaction with one. Further than this, he was able to provoke an abdominal attack with the preparation to which he gave a positive cutaneous reaction, while the others caused no ill effect. He was evidently sensitive to some impurity contained in the one preparation. The impracticability of standardizing such an impurity for use in cutaneous testing is self-evident.

In citing this case, I do not wish to be taken as advocating inaccurate methods when accurate methods can be used. I simply advocate inaccurate tests, rather than no tests at all and admit the unavoidable inaccuracy of our present methods.

### Tests with Solutions

One frequently wishes to test a patient with some substance for which he has no stock solution, such as a certain variety of straw, clover, newspaper, a dress, carpet, upholstery and dust. Suitable

extracts of such substances can often be made by allowing them to stand several hours in a solution such as that described by Clock or by Wodehouse and Olmstead, or in Coca's solution. Solutions should then be filtered for the sake of sterility through a Bergfeldt filter. It is usually impossible to standardize a solution of this sort, since the offending element is a totally and hopelessly unknown quantity. For the sake of safety, it is often advisable to make serial dilutions, especially in the case of highly sensitive individuals and use dilutions too small to be harmful.

It is hardly necessary in a work of this scope to describe in detail the methods of preparation of test solutions. This has been admirably done in recent articles by Clock, Coca, and by Wodehouse and Olmstead. It may be well, however, to mention the fact that in making a preparation for cutaneous testing one should endeavor to obtain the suspected substance in relatively concentrated form. If an individual is thought sensitive to emanation from clover, the extract should be made of the whole, unbruised stem, leaf, or flower, the idea being to get in solution a maximum quantity of the substance contained in the outer part of the plant. In the case of food hypersensitiveness, the inner portion of an article is less likely to be the important factor than the outer. In this case, however, maceration of the whole article before extraction is desirable. One must add here that efforts at purification of any extract are always inadvisable. Purification would be the logical thing if one knew the particular constituent responsible for illness. When an individual is sensitive, however, to a substance such as grain, it is impossible to surmise at the outset what substance is primarily responsible and where it is located so that in process of purification the real offender might be lost.

While purification of an extract is, in general, inadvisable, the use of purified extracts often gives useful information in the case of sensitiveness to common foods, such as egg, milk, or wheat; that is, to foods which are used so frequently in cooking as to be difficult to avoid. In the case of egg, if a person is proved sensitive to either egg white or egg yolk alone, the offending substance can often be removed mechanically, and the remaining portion of the egg can be used. Furthermore, cooked egg (coagulated protein) in this case may be tolerated. This information may enable a person to use cooked egg, cake, and coffee in which egg is used in the clearing. In this case, the avoidance of egg is no real hardship. In the case

of the ovomucoid fraction, which is not destroyed by heat, it may be necessary for the patient to avoid not only raw egg but cooked egg as well, in fact, occasionally, every food which contains even a trace of cooked egg and in three cases known to the writer, also hen meat. Likewise, in the case of sensitiveness to the lactalbumin fraction of milk, milk can often be rendered harmless by such a simple measure as boiling; while sensitiveness to the casein fraction may necessitate the discarding of milk altogether. Patients sensitive to certain raw foods are very often insensitive to the foods when they are thoroughly cooked and vice versa. A knowledge of this may be of great convenience in choosing a diet.

It must also be emphasized that in making solutions either for testing or treatment, an effort must be made to use the substance in exactly the form in which it causes reaction and often material obtained from a certain limited source. For example, one patient sensitive to egg in cake and noodles, reacted very little to raw or boiled egg and Meixner's patient sensitive to salted roasted peanuts did not react to raw peanuts. One of my cases sensitive to Iva xanthiifolia collected in a neighboring state did not react to a concentrated extract of the same pollen collected here.

Pollen, fish glue, cottonseed, flax, some of the animal danders, and other air-borne agents should not be handled as promiscuously or in the same concentration as food extracts. These agents are, as a rule, stronger and provoke more severe reactions, and give convincing results when used in more dilute solution. This is probably because of a smaller admixture of inert agents, such as are contained in food extracts. Pollen extracts of a strength of 0.01 mg. of dry pollen to each cubic centimeter is often sufficiently concentrated to give marked reactions in sensitive individuals. Frequently solutions of a strength of 0.1 mg. to the c.c. or even 1.0 mg. to the c.c. are required, however. In group testing, usually a concentration of 0.1 mg. to the c.c. of each individual pollen is adequate and solutions stronger than this should not be used in routine practice.

## Preliminary Group Tests

The procedure of intracutaneous testing can be shortened and simplified through the use of preliminary group tests; that is, through the use of mixtures of from five to eight extracts. In the group tests, it is advisable to use less of each individual substance

than in the making of individual tests. I use no more of the mixture than of the individual solutions in the final tests.

Preliminary tests made in this way often enable one to say that a patient is sensitive to a certain mixture of pollen, vegetables, grains, animal dander, or sea foods. Further tests can then be made with each extract contained in the mixture giving positive reactions, and frequently a great deal of time and trouble for the patient can be saved.

One might be inclined to criticize the use of group tests because of the large number of extracts used in each solution. When one uses individual tests, however, he should not deceive himself to the extent of believing he is using solutions containing few substances. I should guess that the average solution used in skin testing contains over one thousand different substances. The use of eight thousand in a group solution should not add much to the inaccuracy of this already inaccurate method. Its simplicity should offset this error.

No hard and fast conclusions can be drawn from preliminary group tests. It is simply a useful means of getting a clue. One often finds that a group reaction comes out more strongly positive than tests with any individual member of the group, and vice versa. One should not let a negative group test interfere with his trying any individual constituent of a mixture should he suspect it as a cause of illness.

Cooke has very properly warned against the use of a large number of tests at one sitting. I have employed the method described above for several years, using often more than 300 extracts at one sitting and have had very few severe constitutional reactions. I have been very careful, however, with certain patients, especially those in whom sensitiveness to pollen, glue or hair is suspected. The use of a large number of extracts to which a patient does not react should have little or no ill effect.

## Dangers of Reaction

Before leaving this subject, one should again warn of the danger of violent constitutional reactions which occasionally follow intracutaneous injections. One should have epinephrin and atropine on hand ready for quick use, and should use it immediately and freely if coryza, asthma, generalized erythema or itching of the

skin develops. Patients should not be allowed to leave the office sooner than one-half to one hour after the tests are completed and should then be warned of the possibility of a reaction appearing even later.

### One Syringe Method

It is rather impracticable for the profession generally to use a large number of syringes and needles in making intracutaneous tests; and it is unnecessary. In my work, I use one syringe and one needle. After making an injection, I wash it thoroughly in each of three vessels containing sterile salt solution. The first vessel dilutes the extract greatly, the second more still, and the third to such an extent that any trace which remains in the syringe is too dilute to interfere with the accuracy of subsequent tests. The third water is not contaminated sufficiently to interfere with the use of the same three solutions for further washing of the syringe; that is, if the three vessels are always used in the same rotation. If one wanted to be more careful, he could do so by using four or five vessels of salt solution instead of three. This is unnecessary, however, if one is thorough in his washings. I frequently find one test intensely positive and the next negative, proving thus that the cleansing of the syringe must have been adequate.

### Interpretation of Skin Tests

One's first impression of skin testing is likely to be one of disappointment. If he is so unfortunate as to be seriously misled by them, the first impression may be one of disgust. The fault lies more often, however, in the interpretation of results than in defects in the method itself.

In order to interpret correctly, it is necessary to bear in mind two facts: (1) that a strongly positive cutaneous reaction with a given substance does not by any means indicate that it is responsible for an illness, and (2) that a negative reaction with a given substance does not exclude it as a cause of illness.

**False Positive Reactions.** Sensitive patients usually give positive skin tests to a large number of extracts (20 or more). They usually react clinically to very few of them—in fact, not often to more than two or three. A positive reaction indicates simply that the skin is sensitive to a given substance as used in testing. It

does not indicate that the patient is sensitive to the substance as encountered in natural ways. In other words, the patient, although actually sensitive, may tolerate the substance as encountered naturally, and in the dosage encountered naturally.

CASE 22.—*Examples of Multiple Skin Sensitiveness in the Absence of Clinical Sensitiveness.*—One patient subject to no apparent illness, except autumnal hay fever, gave intensely positive intracutaneous reactions to each of about twenty spring and fall pollens; to several specimens of animal hair, and to a number of extracts of fruits, vegetables, and grains. He was ill, so far as one could judge, only in the fall, and could relieve himself by a change in geographic situation. He was evidently sensitive to many substances, but his clinical tolerance was such that none except fall pollen as encountered in one small district made him ill.

A somewhat different type of case is that of a patient with active tuberculosis who was subject to asthma, regardless of season or geographic situation. She gave positive skin tests to a number of extracts including wheat. Avoidance of wheat in the diet gave her no relief whatever, but avoidance of contact with flour (inhaled while making bread) gave her great relief, even when she ate wheat bread freely.

This finding of reaction caused by the inhalation of wheat flour with tolerance for wheat taken by mouth might be explained in several ways. It is possible that the nasal mucous membrane was intolerant of wheat flour when inhaled, but was tolerant of the small amount reaching it through the blood stream after the ingestion of wheat. It may have been, on the other hand, that the flour was so changed by cooking or by digestion that the product to which she was actually sensitive was destroyed.

**False Negative Tests.**—Patients proved clinically sensitive to a given substance often give negative intracutaneous reaction to an extract. This condition is encountered more frequently in older individuals than in children; also, more frequently in individuals whose symptoms occur as a result of a general reaction than in individuals sensitive to air-carried substances. For example, a negative reaction is found more often in patients who have asthma, hives, or angioneurotic edema caused by ingestion of egg (general reaction) than in patients who have hay fever or asthma caused by local contact of the respiratory mucous membrane with pollen or emanations from animal hair.

In searching for an explanation of this fact, it might be mentioned that patients sensitive to a food can be sensitive to the food as it exists in a natural state or after it is changed by heat or by its mixture with other substances in prepared foods, or to some product elaborated during its digestion or putrefaction in the ali-

mentary canal, or to some product formed by parenteral alteration of some of its products after absorption. A patient with egg urticaria may be insensitive to egg but sensitive to a product formed from egg after many catabolic and anabolic processes. One patient with egg asthma who gave a very slight skin reaction, was clinically so sensitive to egg that three drops of a solution of egg made by diluting one drop of fresh mixed egg with 200 c.c. of water was sufficient to cause severe asthma, if taken by mouth. The same result appeared after the subcutaneous injection of 0.0001 mg. of whole egg. The reactions produced in either way did not appear sooner than thirty-six hours after the treatment with egg.

The mere fact that the nasal mucous membrane or gastrointestinal mucous membrane is sensitive to, and reacts to, a given substance does not necessarily mean that the skin is sensitive and should react positively. It is simply good fortune that the skin does react positively so often.

Given the facts that a negative skin reaction does not exclude a given substance as a cause of illness and that a positive reaction, although indicating sensitiveness to the substance, does not indicate that it is a cause of illness, the following general rules are of value in interpreting results:

1. When skin tests give large hive reactions with pseudopods it can be assumed that the patient is of allergic strain and probably hypersensitive to some material substance.

2. Occasionally, the skin reacts to one substance only. This is rare. When this is the case, the real offender, often, is discovered.

3. The skin in sensitive cases usually reacts to a large number of substances and often to several groups of substances. When this is the case, the larger wheals usually indicate the greater offenders. This is the rule but is by no means invariable. A patient may react markedly to vegetables and slightly to grains and be made actually ill by a grain only. The fact that extracts prepared for cutaneous testing contain a large variety of chemical bodies may account for this circumstance. The agent responsible for an illness may be the largest constituent of the mixture or the smallest constituent. If the offending substance is the smallest constituent, the skin reaction may be less marked than that produced by mixture containing a less offensive agent in large amount.

CASE 23.—*Clinical Sensitiveness in the Absence of Skin Sensitiveness.*—A woman who had been subject for months to almost daily spells of abdominal pain and vomiting, was emaciated and seemed unable to tolerate any type of diet which was chosen for her. She gave positive intracutaneous reactions to almost every type of food, although to some much stronger than others. After many combinations of food in the diet had been tested without benefit, she was put on a diet confined to meats and fruits. She was absolutely free of symptoms while on this diet and gained rapidly. Many attempts were made to add to the diet but without success. The least digression caused immediate recurrence of vomiting and pain. Milk and eggs, which did not give strong skin reactions, were not tolerated even when taken in small amounts.

Although the foregoing facts may be disturbing to those enthusiastic over the possibilities offered by cutaneous tests, they are less disturbing than error; and if one bears in mind the fact that positive skin tests do not indicate sensitiveness to an agent as it is encountered in nature, one can often gain many useful clues without being seriously misled. A clue gained from a skin test should never be looked on as diagnostic but should be used as a clue only. The diagnosis should be verified by and based on history and examination, and on other tests to be mentioned subsequently.

## Ophthalmic and Nasal Tests

The ophthalmic and nasal tests are especially useful in picking out pollens or other air-carried substances responsible for hay fever and asthma. These tests should be made only after the results of skin testing have been observed. The ophthalmic test can be made by spraying pollen solution (1:1,000 extract from dry pollen) into the conjunctival sac. A positive reaction is indicated by redness of the conjunctiva and increased lacrimal secretion which persists for more than five minutes. Momentary redness cannot be considered positive. The effect of a positive reaction may be immediately relieved by instilling a drop of epinephrin (1:1,000 solution) in the conjunctival sac.

The nasal test is made by spraying a pollen solution (1:1,000 solution) into the nose. A positive reaction is indicated by sneezing, swelling of the nasal mucous membrane, and watery or clear mucous secretion which persists for several minutes or more. The ill effect of this reaction can also be relieved by the local use of epinephrin.

These tests are especially useful in pollen cases, and with their

aid one can often pick out from a group of pollens which give positive cutaneous tests the one particular pollen responsible for clinical symptoms.

Case 24.—*Illustrating the Greater Specificity of Conjunctival Tests.*—In a patient who gave positive intracutaneous tests to almost every fall pollen which was used in testing, Ambrosia elatior was the only one of the group which caused a positive ophthalmic reaction. She was treated with Ambrosia elatior extract for several months before the hay fever season began and was apparently rendered so tolerant of this pollen that, although she continued to give a positive skin reaction to it, she remained symptom free during the entire season. The inference might be drawn in this case that, although she was sensitive to many pollens before treatment, tolerance for all except Ambrosia elatior was such that she could stand without difficulty the amount encountered naturally in her ordinary habits of life.

Ophthalmic and nasal testing is limited in usefulness because relatively few tests can be made on a patient in one day. A positive reaction prevents further use of the eye for testing for a day or two. A negative reaction does not interfere with further testing, and often if one suspects one of a group of, say, six different pollens, the entire six may be tried, provided the one which gives the positive reaction happens to be used last.

Patients who are clinically sensitive to a pollen usually react positively to a 1:1,000 solution. Occasionally they do not. It is possible that stronger solutions might be used in an effort to provoke a positive reaction. I have not studied this point, since a majority of patients do react to the solution as described. It is not out of line with our knowledge of facts that patients who fail to react to a 1:1,000 solution of a given pollen extract can be actually clinically sensitive to the pollen as encountered in nature. It must be borne in mind that during the pollen season, the conjunctivae encounter pollen dry and untreated. It is not difficult to conceive that the exposed tissues might react to dry untreated pollen even though insensitive to pollen in high dilution.

### Inhalation Tests

Nasal tests are also useful for testing in a simple way for sensitiveness to animal hair, feathers, or emanations from vegetable matter. The test can often be made by having the patient inhale from the substance to be tested and noting whether or not it causes sneezing or other symptoms resembling hay fever or asthma.

I obtained a very convincing reaction in a carpenter who was troubled with nasal and bronchial reaction while in his workshop. He had a violent attack of sneezing when asked to inhale from a bag of birchwood shavings. The inhalation from shavings of seven other woods caused no symptom whatever. It is often possible to get reactions of this sort with feathers or furs, or sometimes with solutions such as perfume, cedar oil, turpentine, smoke, and like substances.

One must carefully discriminate between patients who are actually specifically hypersensitive to a substance of this kind, and those who have nasal reaction due to other causes and who give a positive test due to the nonspecifiic irritating effects of the substance as used in the test. Patients with pollen asthma will occasionally be made to sneeze or to suffer an aggravation of their symptoms if they inhale perfume, smoke or dust. The inhalation of these substances, however, may have no untoward effect on them except during the pollen season. In other words, though made worse by their inhalation, these patients may not be actually specifically hypersensitive to them alone. However, the chance of combined sensitiveness in cases such as these is always a possibility and may prove to be the rule.

## Subcutaneous Tests

Subcutaneous tests have their greatest sphere of usefulness in confirming a given diagnosis. Their use is rarely necessary, however. If one suspects Ambrosia elatior as a cause of hay fever, and can inject a small quantity of Ambrosia elatior pollen extract subcutaneously during a well period and reproduce the symptoms of hay fever, he should feel convinced that this pollen is the probable cause of illness. Similarly, if one believes sensitiveness to milk is responsible for abdominal pain or bladder disorders, and can reproduce these symptoms during a well period by subcutaneous injection of milk, he should feel that he is on the right track. Tests of this sort are frequently obtained during specific treatment and tend to verify a diagnosis.

In order to prevent severe constitutional reactions, subcutaneous tests should be used with great care, if at all, and only minute amounts should be injected. If one suspects milk as a cause of asthma, not more than 0.0001 c.c. of milk should be given

subcutaneously as an initial dose. If this should fail to produce asthma, a larger dose might be administered. The ill effect of a reaction can be combated almost immediately, as a rule, by the subcutaneous injection of 0.5 c.c. of epinephrin (1:1,000 solution). If there are no signs of relief within two or three minutes, the administration of epinephrin can be repeated at from two to five minute intervals until relief is obtained.

### Clinical Proof of Diagnosis

Whereas the preceding tests may give useful clues, they do not prove a diagnosis. Proof, such as it is, lies finally in clinical tests. If one has discovered the offending agent, the patient should be relieved by its removal and symptoms should recur during a well period when he is again brought in contact with the suspected substance in a natural way. This is not proof, but is the best that can be obtained by practical methods of testing at our disposal at the present time.

### Summary

Specific hypersensitiveness may be suspected in any person who has in his family or personal history, or who on physical examination shows certain rather typical manifestations of the condition, such as the ocular, nasal, pharyngeal, bronchial, or cutaneous symptoms of reaction. It may be suspected in patients who show certain less characteristic symptoms, if no other adequate cause for the disorder is found on examination, symptoms such as the gastrointestinal, and bladder symptoms; headaches; nervousness; asthenia; hypotension; which have been alluded to previously. The foregoing symptoms suggest the possibility of hypersensitiveness, especially when they occur in the absence of other adequate causes of illness, and when the family or personal history is positive.

In searching for the source of reaction, or rather for the specific agent primarily responsible for an illness, careful observation by the patient is helpful and often makes complete study and a correct diagnosis possible.

Specific tests are often useful in gaining a clue as to the source of illness. The cutaneous tests are useful in young persons or in persons sensitive to air-carried substances. The intracutaneous are more useful in the less sensitive persons, i.e., older patients, those

sensitive to foods, and those whose symptoms occur as part of a general reaction. Intracutaneous tests often result in positive reactions in patients who are not sensitive to the agent as encountered in nature, and vice versa, persons who are sensitive to certain substances as encountered naturally do not always give positive skin reactions. For this reason, care should be used in the interpretation of skin tests, and a diagnosis should never be based on the results of these tests. Positive results should be used as a clue only and should be verified by other special tests, such as the nasal and ocular tests, and by subcutaneous or clinical tests.

Secondary factors may modify the symptoms of reaction, such as infectious diseases, functional or organic diseases, reflexes, agents which irritate or stimulate either mechanically, chemically, or otherwise, so that a diagnosis should be based, if possible, not only on the history of a case and physical examination, but also on the apparent finding of the specific agent responsible for illness, on removal of the agent with relief of symptoms, and, finally, on a reproduction of symptoms during a well period by bringing the patient again in contact with the suspected substance. Relatively few mistakes will be made when these procedures can be carried out fully, and when conclusions can be based on adequate data.

## CHAPTER XVI

## SPECIFIC, NONSPECIFIC, AND SYMPTOMATIC TREATMENT

Illnesses caused by hypersensitiveness to foreign substances can be treated along five different lines; namely, avoidance or removal of the specific cause of illness; avoidance or removal of contributory causes; specific protein treatment; nonspecific protein treatment; and symptomatic treatment.

Each of these methods is important. The choice depends upon the severity of the illness, upon the degree of hypersensitiveness, and upon the nature of the substance to which the patient is hypersensitive. In the majority of cases, two or more of the above measures can be used to advantage.

The simplest method is best when the simplest can be used—namely, avoidance or removal of the specific cause of illness. However, removal of the specific cause is often difficult or almost impossible. This is often true in the case of sensitiveness to the common pollens, to wool, to common foodstuffs (such as cooked milk, eggs, sugar and wheat), to miscellaneous substances which occupation often brings a patient in contact with, and to substances which cannot be discovered by means at our disposal. In these instances, one or more of the latter four measures must be chosen.

### Local and General Reactions

Having ascertained the fact that a patient is sensitive to a certain substance, it is important to know whether the clinical symptoms occur as a result of direct contact between the substance and the affected tissues, or occur as part of a general reaction. For example, in the case of asthma caused by sensitiveness to wheat, it is important to know whether the respiratory symptoms result from direct contact between the mucous membrane of the bronchial tubes and wheat flour inhaled, or whether they occur as part of a general reaction due to the ingestion of wheat bread. In the former case, bread can be eaten with impunity and the patient, to be relieved, needs only to avoid contact with wheat flour. In the latter case, it may be necessary to remove wheat from the diet.

It is, furthermore, important to know whether an individual is sensitive to a given substance as encountered in its natural state only, or whether he is also sensitive to the substance after it has been treated for use. For example, an individual sensitive to the lactalbumin fraction of milk is made ill by raw milk,

but may tolerate unlimited amounts of cooked milk. In the case of sensitiveness to egg white, an individual can often tolerate cooked egg. In sensitiveness to the ovomucoid fraction, however, he may be made ill by either raw or cooked egg.

The ocular, nasal, and bronchial symptoms, and eczema confined to the hands, face, and ankles are in the majority of cases attributable to direct contact between the mucous membrane or skin and the substance to which it is sensitive if it occurs as an isolated symptom. These symptoms may also occur, however, as part of a general reaction.

Urticaria, angioneurotic edema, generalized dermatitis, irritable bladder, hypotension, and neurologic manifestations usually occur as part of a general reaction. Air-carried substances are rarely absorbed in sufficient quantity to give rise to these general symptoms, although this does actually occur occasionally. As an example, I may mention a case of autumnal hay fever in which the dominating symptoms were neurologic.

Gastrointestinal manifestations may result from either local contact of the mucous membrane with a food or may occur as readily as part of a general reaction after absorption of an offending food product.

A symptom such as asthma, is frequently associated with other manifestations of general reaction such as hives, and angioneurotic edema, when it occurs as part of a general reaction. This is not true of the same symptoms, asthma, when it occurs as a local reaction, that is, as a result of local contact between the bronchial mucous membrane and air-borne substances. Bearing in mind this general rule, it is often possible to surmise correctly that a symptom, such as hay fever, or eczema, is due to exposure to some air-carried substance or to some product which has been distributed by the blood. A knowledge of this fact is often useful in the attempt to relieve the patient.

## Avoidance of Cause

Avoidance of cause is often simple if one knows the nature and whereabouts of the substance responsible for reaction. It is difficult if its distribution is only partly known. For example, a patient previously mentioned who was sensitive to whole egg, cooked or raw, continued to have symptoms occasionally after egg was apparently removed from the diet. It was eventually found that she was sensitive to hen meat but could easily tolerate rooster meat. The occasional attacks which occurred while she was on an egg-free diet were traced to the egg in hen meat. It is not uncommon for patients sensitive to products of vegetable life to react to the traces of such substances contained in milk and for buckwheat cases to react to the traces contained in honey. Avoidance of cause is difficult, therefore, unless the distribution of the agent causing the reaction is known.

**Pollen.**—Pollen can usually be avoided by a change in geographical situation. In the case of sensitiveness to light air-carried pollen of the common weeds which pollenate over a long season, complete avoidance can hardly be accomplished otherwise. Pollen can be avoided in sufficient degree to give relief in mild cases by removal of the common weeds of the neighborhood, by having the patient confine his activities to down town districts, by avoidance of trips into the country, by having him live and work on the upper floors of office buildings or hotels, and by having him keep the windows closed. This often gives partial or complete relief in mild cases, except on windy days when the air is filled with pollen even at the top of high buildings. Scheppegrell's ingenious experiments have shown the marked effect of air currents on the distribution of pollen in the air at different heights. On windy days he found pollen almost as abundant at a height of five thousand feet or more as it was within a short distance of the ground. This, however, would not apply to an environment near a ragweed patch.

In the case of sensitiveness to rare pollens, such as coreopsis, relief can easily be obtained by avoidance of districts in which the flowers grow profusely, or by having them removed from the immediate vicinity.

**Products of Vegetation Other than Pollen.**—Products of vegetation other than pollen can usually be avoided easily if the source of the illness is recognized. Orris root is worthy of especial mention since this product is so widely used in the manufacture of perfumes, flavoring extracts, toilet articles of all sorts, including tooth paste, face powder, face cream and soap.

In the case of sensitiveness to the stalk or leaf of plants, such as clover or straw, the offending substance, as a rule, can be avoided sufficiently to relieve symptoms if the patient is aware of the source of his trouble. Clover, on account of its profuse growth, is difficult to avoid entirely; but, according to my experience, the degree of sensitiveness is not extreme in grade so that its complete avoidance is not necessary.

The essential oils and other products of plant life, such as turpentine, cedar oil, the oils used in perfumes and flavoring extracts, also the products derived from coal, such as benzol, and those derived from crude oil, such as gasoline, can usually be avoided easily if recognized as a source of illness.

**Food.**—The symptoms of food idiosyncrasy usually occur as part of a general reaction to a food or a split product. In the case of sensitiveness to uncommon articles of diet, such as tomato, onion, and cabbage, avoidance is simple. When a patient is sensitive to articles used so commonly in cooking, as milk, eggs, or wheat, avoidance is difficult, especially if he is sensitive to the cooked as well as the raw product. It is rarely advisable to attempt specific treatment in food cases except when the patient is sensitive to foods so commonly encountered as cooked milk, egg, sugar or wheat.

**Animal Products.**—It is rarely advisable to treat specifically for sensitiveness to animal dander such as horse, cat, or dog, since the animals and their pelts can usually be avoided. Specific treatment would seem justified only in the case of wool sensitiveness and in cases where occupation necessarily brings the patient into contact with animals to which he reacts. In several cases of sensitiveness to wool (all eczemas) observed by the writer, the symptoms were not severe and were relieved through the use of cotton clothing between the skin and woolen garments.

Walker has obtained good results in increasing tolerance for animal dander, by subcutaneous inoculations with dander extracts. He does not recommend this treatment, however, when avoidance is possible.

In sensitiveness to feathers, such as goose, duck, or chicken, relief can be obtained by the use of floss pillows.

**Drugs.**—When individuals are sensitive to drugs, such as iodoform, formalin, novocaine, morphine, aspirin, etc., relief of symptoms can be obtained if the cause is discovered. One is occasionally sensitive to an impurity in a drug. This is important in the case of drugs so useful as acetylsalicylate and arsphenamine, for an individual sensitive to one preparation of a drug can often tolerate other preparations.

**House Dust.**—House dust is worthy of especial mention since it is frequently responsible for house asthma, the importance of which has been especially emphasized by Cooke. Relief in this case can often be obtained by the removal from the house of certain articles of furniture, upholstery, rugs, disinfectants, cleaning fluids, glue, etc.

**Smoke.**—Individuals sensitive to smoke can frequently obtain relief by slight change in environment. One patient who had

asthma, due apparently to gasoline smoke, could invariably obtain relief by moving to a different part of a hotel in which he lived. The room which he occupied at the time of his illness was situated directly over the garage. Individuals sensitive to coal smoke should be cautioned against long railroad trips, since in this position they are frequently exposed intensely to smoke and may suffer a severe exacerbation of their illness. In one smoke sensitive case, a long trip precipitated an attack which nearly terminated fatally.

In one case, previously alluded to, in which sensitiveness was traced to wood smoke, it was found that the patient could live comfortably in steam heated apartments but that she invariably had severe asthma in houses where open fires or furnaces were used. She was so affected even during the summer months when the furnaces were not in use.

**Bacteria.**—Definite symptoms of reaction often accompany acute infectious diseases, such as rheumatic fever and scarlet fever. These manifestations can be treated best symptomatically since they usually disappear spontaneously after the acute illness has subsided. Individuals sensitive to products elaborated in chronic foci of infection, should be treated by removal of such foci. This type of illness, however, seems to me to be rare. When the focus cannot be reached, treatment with vaccines might be justifiable. According to Walker and Rackemann, this method of treatment frequently yields beneficial results. However, one would think in the case of sensitiveness of this sort that the patient would gain tolerance through constant intimate contact with the products of infection elaborated within his own body.

**Therapeutic Sera.**—In demonstrated hypersensitiveness to horse serum, the therapeutic use of horse serum is dangerous even in very small doses and should not be used unless the indications are very urgent. Antitoxins of sources other than horse should be provided for patients of this type. Patients sensitive to horse dander are not necessarily sensitive to horse serum. If there is any question whatever, intracutaneous tests should be made before serum is administered and Coca's method of administration should be employed.

**Blood Transfusion.**—As previously mentioned, I have observed two cases of reaction at the beginning of blood transfusion in which the reactions were believed to be due directly to sensitiveness on

the part of the patients to foods eaten by the donors. The statement, while seemingly fantastic, is actually very true and would seem analogous to the eczema of breast-fed babies caused by sensitiveness of the infant to certain foods eaten by the mother.

It is urgent to inquire for a family and personal history of hay fever, asthma, and hives before transfusion is recommended. In case of a positive history and the indications are urgent, the patient should receive a preliminary dose of adrenalin and the transfusion should be given with great slowness.

**Multiple Sensitization.**—Patients sensitive to a number of substances may tolerate some of them if the others are carefully avoided. For example, many patients with pollen hay fever give positive skin tests to vegetables, fruits, or grains and actually obtain partial relief of hay fever by avoidance of the food products to which they give positive tests. Such substances may have no untoward effect except during the pollen season. One patient with hay fever and eczema was found sensitive, among other things, to a certain silk dress. An extract from the dress gave an intensely positive cutaneous test. It was observed, however, that when her illness was relatively mild, due to the avoidance of other substances which made her ill, she could wear the silk dress with impunity. At other times, however, when she was suffering markedly with hay fever, and dermatitis, contact with the dress invariably caused itching and an increase in the rash and asthma.

**Summary.**—To recapitulate, the avoidance or removal of the specific cause of reaction is the simplest, surest and safest method of treatment when this can be accomplished. It is only in cases where the specific cause is not discovered or cannot be removed that the measures to be described subsequently need be resorted to.

### Removal of Contributory Causes of Reaction

Very frequently it is impossible to discover the specific substance primarily responsible for reaction. In this case, removal of certain contributory causes may relieve the patient partly or completely.

**Physical Factors.**—Physical factors, such as light, heat, cold, mechanical and chemical irritants, and functional activity, frequently influence the symptoms of reaction and often determine their site of localization. The untoward effect of physical factors has been

mentioned by many observers and is noticed by a large proportion of sensitive patients. For example, patients subject to urticaria are frequently relieved to a marked extent by the removal of agents which irritate the skin mechanically; by the avoidance of agents which cause increased activity of the glands (sweating); by protection of the skin from heat or cold, and by the avoidance of irritating lotions.

Similarly, patients who have dyspepsia and abdominal pain as a result of alimentary reaction, can often obtain partial relief by the avoidance of foods, such as nuts, which irritate mechanically; by the avoidance of substances such as coffee, salt, and alcohol, which stimulate functional activity; by the avoidance of condiments, such as mustard and pepper, which irritate chemically.

Likewise, patients who have asthma are often relieved to a marked extent by the avoidance of dust and irritating vapors, and exposure to heat or cold.

Whereas physical factors no doubt add in a purely physical way to symptoms caused by sensitiveness to other agents, this should not give rise to doubt as to the existence of specific hypersensitiveness to the action of physical agents to be discussed subsequently. I am by no means certain that the facts above cited are not in reality traceable to the effect of combined sensitiveness.

**Pathologic Factors.**—Patients who are ill with symptoms of reaction (especially general reaction) are usually made worse by additional illnesses. Occasionally, however, they are relieved completely by another disease. I have observed four cases of chronic perennial asthma who apparently were permanently relieved by severe infectious diseases—erysipelas in three cases and scarlet fever in one. I have frequently observed complete temporary relief during the course of an acute infectious disease, even during an attack of pneumonia. This may be accounted for possibly on the basis of heat sensitiveness (see Part II). For example, a case of chronic urticaria caused by heat sensitiveness, was temporarily relieved during the febrile period of an infectious disease. Relief could be attributed in this case directly to fever since the patient reacted to heat only when the temperature was subnormal.

Frequently chronic asthma or urticaria starts soon after an operation. This is such a common experience that surgeons should hesitate to operate upon patients of allergic strain. Occasionally

the reverse is the case—that is, relief follows an operation. Walker mentions a case of asthma relieved by a hernia operation. In one of my cases, chronic urticaria was relieved by a hemorrhoid operation. Alimentary reactions are usually made worse by ulcer, gall bladder disease, or chronic appendicitis. Very often partial or complete relief can be obtained by treatment of these conditions.

Dysfunction in the glands of internal secretion, which is rather frequently noticed in cases of general reaction, often adds to the severity of the illness, and treatment of these conditions occasionally gives partial relief.

**Summary of Contributory Causes.**—To recapitulate, when one fails in his effort to find or remove the specific cause of illness, frequently his best recourse lies in the discovery and treatment of other abnormalities and illnesses with which the patient may be afflicted. A serious, careful effort in this line often gives relief, which can be obtained in no other way.

### Specific Protein Treatment*

In view of our knowledge of the tolerance which can be developed in patients or animals for living bacteria by subcutaneous inoculation with their products, and in view of the fact that hypersensitiveness to serum in animals can be completely removed by inoculations with serum, it has been quite natural that many investigators working both jointly and independently should have tried this method of treatment on human beings sensitive to pollen and other bodies not of bacterial origin.

It is good fortune that tolerance for foreign substances can frequently be developed in this way in sensitive patients, and it is surprising that statistics published by different writers using different plans in therapy agree in the essentials concerning the results which can be obtained. For the many names and researches responsible for the development of this line of knowledge, the reader is referred to the authors mentioned in the bibliography.

**Pollen Treatment.**—The practical development of this line is a result of the effort of many investigators, among the earlier of

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*Pollen solutions for treatment are put out by the commercial laboratories mentioned on page 201. If one wishes to obtain the best result in a high percentage of cases with commercial extracts, he should endeavor to get serial dilutions, the strongest of which is from 1 to 5 per cent, depending upon the district in which the patient resides—that is, upon the pollen content of the air. The time interval between doses for the average case should be not more than one day for the smaller doses, two days for the more concentrated solutions, and three to seven days for the most concentrated extract.

whom may be mentioned Curtis, Dunbar, Noon and Freeman, Koessler, Lowdermilk, Rackemann, Walker, Cooke, Scheppegrell, Goodale, and others.

It gives me great pleasure to cite especially the work of my friend, Dr. R. Claude Lowdermilk of Galena, Kansas, who first interested me in the possible application of the theories of anaphylaxis to the study of human illnesses. He, working in a small country town and without knowledge of previous work on the subject, conceived the idea that hay fever was a phenomenon of anaphylaxis. He applied Vaughan's theory to the condition and believed that symptoms were due to specific ferments which split certain protein molecules with the liberation of a poison which caused reaction. He developed a method of treatment by subcutaneous injection of pollen extract which is not different from that used generally at the present day. He treated himself, a sufferer for a period of twenty years, and with one season's treatment, succeeded in relieving himself to the extent that he has been not only symptom free for the twelve subsequent seasons, but can actually gather his own pollen without ill effect. This work, carried out between the years 1911 and 1913 was not reported until 1914. His work, therefore, almost coincided in time with the earlier scientific, safe, and successful methods which were reported, namely, those by Noon and Freeman in 1911, and by Koessler in 1914.

The method now generally employed lies in the use of increasing doses of pollen extract given subcutaneously at varying intervals of time. An increase in tolerance for pollen is the result in the majority of cases, with partial or complete relief of symptoms. The writer has used this method each year since 1915, trying different plans in technic each year. The results have been greatly improved each year until last year when practical clinical relief was obtained in almost 100 per cent of cases which were thoroughly treated.

*First Method.*—Whole pollen of small ragweed, large ragweed, and golden rod, equally mixed, ground finely and suspended in Lowdermilk's solution was used for the inoculations. This solution was prepared at frequent intervals due to a belief that pollen solutions had a marked tendency to deteriorate even at ice-box temperature. The maximum dose given was 1mg. of pollen.

*Second Method.*—The second method was like the first except that the solutions were cleared by centrifugation at high speed.

*Third Method.*—Several pollens were each weighed out separately in 10 mg. lots and kept in wax papers in a desiccator. A specimen of each was ground up finely at weekly intervals, suspended in Lowdermilk's solution and given in in-

creasing doses, each patient being given the pollen to which he gave the strongest skin and ophthalmic tests. The use of this method seemed to yield better results than the previous ones and amounted to practical relief in about 40 per cent of cases.

*Fourth Method.*—Each of some twenty pollens, common to this district, were ground up separately with sand in 500 mg. to 5 gram lots, were suspended in Lowdermilk's or Coca's solution, (1 per cent suspension) and clarified after several days by sedimentation. Toluol was added to this mixture (at Coca's suggestion) as a preservative. This preparation seemed to keep potent for several months at ice-box temperature. Its use saved the laborious process of preparing fresh suspensions each week. (NOTE: The plan of making suspensions sufficient in quantity to last an entire season is recommended, since by its use the preparation of fresh stock solutions of somewhat greater potency than the old ones is avoided. Coca's method of filtering his preparations through a stone filter seems a valuable addition in technic, although no infections were obtained through our use of stock solutions as above prepared).

From each stock solution, serial dilutions were made at weekly intervals and kept at ice-box temperature. In the treatment of patients those extracts were chosen for use which produced a positive conjunctival reaction in a 1 to 1,000 dilution. When none of the pollens gave positive conjunctival tests, as happened in several instances, those pollens were chosen which gave the strongest intracutaneous tests. The following plan of administration was used.

Treatment was commenced, when possible, in June. In many instances, treatment was started much later than this, and even at the beginning of, and during, the pollen season. For the initial dose 0.1 c.c. of a solution containing 0.001 mg. of pollen to the cubic centimeter was used in every instance. The injections were given each day and the dose doubled each day, that is, patients were given 0.1 c.c. on the first day, 0.2 c.c. on the second, 0.4 c.c. on the third, 0.8 c.c. on the fourth, and on the fifth 0.1 c.c. of solution ten times as strong, that is, a dilution of which 1 c.c. contained 0.01 mg. of pollen. This increase in dosage and concentration of solution was continued until a dose of 0.25 c.c. to 0.5 c.c. of a 1 per cent solution was reached—that is, a solution of which 1 c.c. contained 10 mg. of pollen. When this, the maximum dose, was reached, the interval was spaced out to from three to six days, and this dose was repeated when possible up until a few days before time for the pollen season to commence. It was then discontinued. When there was need for haste because of the approach of the pollen season, the injections were given twice daily instead of once daily. These patients gained tolerance more rapidly and reacted less, it seemed, than the others.

Patients who failed to show signs of hay fever after the season was well started were given no further treatment. Those who developed hay fever, however, or who seemed to be less than 75 per cent relieved, that is, about 40 per cent of the cases, or who had been insufficiently treated subcutaneously because of starting late, were given local treatments in the following way on the basis of McKenzie's work.

*Local Treatment with Pollen.*—At daily intervals a mixture of several 1 per cent suspensions of the more important pollens of this district, namely, the three ragweeds, cocklebur, sages, marsh elder, and lamb's-quarter, were sprayed

into each eye and into each nostril. Following this there was almost invariably a marked attack of hay fever, which in some instances, required adrenalin locally for relief. After this administration had been given for a few days, the reactions after treatment, almost without exception, became less marked, and after five to ten treatments, disappeared almost completely. At the end of ten treatments, the patients were almost without exception relieved of hay fever, or partly relieved. The treatments were discontinued when marked relief was obtained. The mixture of pollens as above mentioned was used in preference to solutions of the individual pollens because of a belief that pollens other than the ones which gave positive tests might have played contributory rôles in the causation of symptoms. Patients sensitive to pollen not contained in the mixture were treated with the pollens to which they reacted.

**Short Interval Method.**—*Fifth and Most Effective Method.*—(The previous methods were described simply because they were used and found less effective and not so safe as the following.)

Unground pollen was extracted at Coca's suggestion instead of ground up pollen. The former can be filtered off much more easily. A 5 per cent suspension was made in a mixture of glycerin 66 per cent with Coca's solution, 33 per cent. This diluent was used at the suggestion of Harrison who had obtained his idea from the previous work of Clock. Clock, in his work, used a mixture of glycerin 66 per cent and strong saline solution, and suggested this as a good method for preserving specificity of extracts. Rosenow, after using Clock's solution, stated to me that it preserves specificity of vaccines much better than aqueous solutions. These statements are in harmony with my one year's experience with Clock's solution. Pollen extracts made in this way are green in color. Aqueous extracts are brown. This difference in color appears to be the result of some difference in the hydrogen content of the solutions rather than to any difference in material actually extracted from the pollen because if glycerin is added in high concentration to extracts made with Coca's solution, the color changes gradually from brown to green. In my work, a mixture of glycerin and Coca's solution was used in preference to Clock's solution because of the fact that I wished to use concentrated glycerin solutions in my serial dilutions and inject them as such. I was fearful that concentrated salt with concentrated glycerin might act as an irritant although I do not know that such is the case.

To 100 c.c. of solution as above prepared was added five grams of unground pollen. This was kept forty-eight to sixty-four hours in the ice box and shaken repeatedly. It has been shown by Coca that time for extraction greater than this is unnecessary since most of

the reaction-producing substances can be removed from pollen within a period of a very few hours.

After an extraction period of two or three days the solutions were centrifuged unless they had settled relatively clear and were filtered through a Mandler filter for sterility, placed in 100 c.c. bottles under aseptic technic, and kept on ice. At weekly intervals, serial dilutions were made from the concentrated extract in the glycerin solution as above described and as such were used in therapy.

The method was simplified to a great extent by mixing certain concentrated extracts and giving them as such rather than as individual extracts as used in previous years. In the ragweed mixture was used equal mixtures as 5 per cent extracts of large, small, and southern ragweed, cocklebur, marsh elder, and Iva xanthiifolia. In the grass mixture was used the varieties most common in this district, namely, timothy, blue grass, and orchard grass.

The fall patients were all treated in the same way, starting between July 1st and September 15th. July 15th is soon enough in the majority of cases.

The initial dose was 0.1 c.c. of a solution corresponding to pollen .01 mg. by weight to each cubic centimeter of solution. The injections were given twice daily in the beginning of treatment and the dose was doubled at each inoculation until the stronger dilutions were reached, namely, solutions containing 1.0 mg. to the cubic centimeter. At this time, it was frequently necessary to space out the time interval to daily injections or to injections given at two- or even three-day intervals. This varied in different patients. When a dose of one-fourth to one c.c. of a 5 per cent solution was reached, the time interval was spaced out to three or four days and this dosage was continued up until about September 15th, when treatment was discontinued.

Several points in technic are worthy of emphasis. The dose was in no instance repeated until the local effect of the previous one had subsided completely or almost completely. The dose was in no instance increased if the previous one caused a mild constitutional reaction. These rules spared me causing a single severe constitutional reaction.

Treatment was continued well into the pollen season because in the previous year, perfect tolerance which had been established at

the first of the season was lost at the end of the season in four cases so that symptoms recurred toward the end of the season. Last year, when treatment was continued up until September 15th, there was not one single case of recurrence during the season.

Local intranasal treatments with pollen solution was unnecessary with this method as with the previous one.

In previous years, patients who had taken pollen treatment and who had given positive intracutaneous tests to fruits, vegetables, grains, and dander (and this was true of the majority of patients) were asked to avoid during the pollen season those substances to which they gave positive skin tests. Some of the patients noticed on testing themselves out that such substances caused an actual increase in their tendency to hay fever. Others noticed no untoward effect. In the latter case, they were allowed to choose any diet they desired.

In addition to this, patients who had a tendency to have hay fever were advised to wear goggles at times, even at night, especially when they were exposed to pollen on windy days; to avoid pollen as far as possible by keeping in down town districts, keeping the windows closed, avoiding trips into the country, railroad trips, etc., and to apply the following lotion to their conjunctiva and nasal mucous membrane when needed.

Adrenalin 1-1000 solution, 1 c.c.
Dilute acetic acid, .3 c.c.
Resorcin solution, 3%, q. s. 32 c.c.

This advice was rarely necessary for patients who had been thoroughly treated. The fact, however, that such advice is useful to patients who have not been treated thoroughly is very evident to physicians who have had experience in this line of work. For example, two cases, a brother and sister, were treated simultaneously for pollen hay fever. Each received the same treatment precisely. They resided in a house surrounded by ragweed patches. The brother was down town the greater part of the day and the sister was at home. The sister had fay fever and the brother remained absolutely free.

It seems to me to be a proved fact that the cure of hay fever depends upon two essential factors.

*First.*—To have suitable pollen solutions.

*Second.*—To increase the dose to such a point as to enable the patient to tolerate the quantity of pollen with which he comes in contact.

The latter factor varies in different localities. In this locality a 1 per cent solution is not adequate. A dose of one-half c.c. of a 5 per cent solution is adequate in almost every case. In larger cities, the final dose need not be raised so high, I am sure, and in country districts where weeds grow more profusely, I have no doubt that larger doses must be used. This has also been the experience of my friend, Kahn, of San Antonio, Texas, who has an unusually good opportunity to observe the result of pollen therapy because of the fact that the Bermuda grass season in that district is extremely long. He states that every case can be relieved if suitable solutions are used and if the dose is raised high enough. Furthermore, he states that the duration of complete immunity is frequently not in excess of six weeks. This corresponds to the interval upon which I can rely. Relative immunity, however, has persisted in many cases for two or more seasons and in a few cases for many years.

The above plan of treatment is not recommended to physicians who are not thoroughly experienced in the use of pollen because of the fact that if technic is imperfect, pollen reactions can be severe, alarming, and even dangerous. Whereas I have never as yet had a mishap in pollen therapy, I attribute this to the fact that I have been extremely careful in my technic.

The above plan is safe, however, I am sure, in the hands of physicians who are experienced in pollen therapy—in fact, is much safer, I am sure, than routine skin tests and is also safer than the long interval methods which I employed previously. My reactions have not been obtained with high doses of pollen given according to any of the methods nor have they occurred in patients in whom the plans were carried out according to rule. Reactions occurred usually with the smaller doses and in patients who did not take treatment regularly. Patients who stop treatment for two weeks or more are likely to react strongly when therapy is resumed unless the dose of pollen is greatly reduced.

**Theoretical Basis for the Short Interval Method of Treatment.**—Upon first thought, one is likely to believe that pollen therapy is analogous to desensitization in the case of serum sensitiveness. Un-

fortunately, this is not a fact. According to Besredka's method, an animal sensitized to horse serum can be desensitized quickly by the giving intravenously of infinitesimal doses of horse serum, increased and repeated at intervals of a few minutes until a large dose is reached. In animals, complete desensitization can be affected within a period of an hour or so. In human beings, however, sensitiveness to foreign agents is unquestionably greater than that ordinarily observed in animals. Furthermore, it is much more difficult to desensitize and an effort to desensitize rapidly is ever so much more dangerous. For this reason, Besredka's method has not, to my knowledge, been attempted in the treatment of human beings. A case has been reported recently in which severe reactions and death followed the intravenous use of pollen.

Upon first thought one might believe that pollen therapy is analogous to vaccine therapy. One might be inclined, therefore, to follow methods learned from the much used vaccine therapy or tuberculin therapy. Here, again, lies an error. Pollen therapy and vaccine therapy are quite different. The reaction from vaccine injections appear slowly—that is, after a period of hours. Also, the immunity gained appears slowly—that is, after a period of hours or days. Furthermore, the period of immunity lasts longer—that is, for a number of days. Reactions in pollen cases, however, appear quickly (within a matter of minutes) disappear more quickly (within less than one hour as a rule), and finally, the immunity gained does not last so long. For this reason, one should expect theoretically that the optimum method of giving pollen injections would be frequently, instead of at the long intervals (three to five days) used in tuberculin therapy. It is in this way that I account for the frequent reactions which I have had during my use of long interval methods employed in previous years. Not only were constitutional reactions more frequent, but local reactions on the arms were much larger. After the use of an infinitesimal dose of pollen, the tendency to react occurs quickly, is over quickly, and the immunity derived from it is probably at a maximum within a period of hours. Therefore, the optimum time to increase the dose and repeat it should be within a period of hours—that is, on the same day. As larger doses are reached, the time interval can be ex-

tended and when very large doses are administered, the interval can be extended to a period of several days.

Walker states that a dose should not be repeated if the local effect of the previous one is as large as a hen's egg. During an entire year's experience with the therapy as above outlined, I had very few local reactions which compared in size with this. Surely, the short interval method should be the method of choice.

### Precautions Suggested for the Avoidance of Reaction

If the following precautions are used, reactions should be few and far between and mild.

1. Before pollen solution is injected, the piston of the syringe should be withdrawn strongly and in case blood enters the syringe, it should be withdrawn and reinserted. Many of the intense reactions are caused, I believe, by the injection of pollen solution into a venule or capillary.

2. Patients should be kept in the office after treatment for one-half hour or preferably more, and in case symptoms of reaction, such as sneezing, itching of the eyes, wheezing, or itching of the skin, are noticed, 1 c.c. of adrenalin should be administered subcutaneously immediately.

3. The dose should be increased with regularity. The dose should be doubled at each inoculation if the patient tolerates it. In case he does not tolerate so rapid an increase, the rate of increase should be reduced to a 75 per cent, 50 per cent, or 25 per cent.

4. The time interval should be regular and in patients who have discontinued treatment for a week or more, the dose should be greatly reduced—in fact, it is almost safer to start treatment again.

5. A dose of pollen extract should never be repeated unless the local effect of the previous dose has almost entirely disappeared.

6. A dose should not be increased if the previous one gave rise to slight constitutional reaction. In this case, the dose should either be repeated or reduced.

7. One must be certain of the potency of the solutions used. If a solution is used which has lost its potency and later a fresh, potent solution is substituted, the dose of potent extract may be enormously increased without the physician's knowledge and a severe reaction may ensue. For this reason, a sufficient quantity of concentrated pollen extract should be made up at the beginning of the

season to last the entire season. Serial dilutions can be made from this as needed. If a fresh stock solution must be made during the season, the dose administered should be greatly reduced. It can be again increased rapidly so that as a rule little time need be lost. A warning against the use of large doses of freshly made solutions cannot be urged too strongly. Unfortunately, the potency of a pollen solution is an unknown factor unless tested upon a patient and even then its potency is unknown except for the patient tested. Freshly made solutions should never be started in high dosage.

### Advantages of the Short Interval Plan of Treatment

This lies chiefly, it seems to me, first, in its safeness; second, in the rapidity with which patients can be given tolerance to pollen. The long interval method requires months. The short interval method weeks. It is impractical to keep out-of-town patients in the city for months in order to protect them from a pollen season which is about equally as long. I have found even among Kansas City patients that few are willing to take treatment consistently over a period lasting from May until September, which is the time frequently recommended for the long interval method. By the short interval method, a high grade of immunity can usually be established within two or three weeks and it is almost needless to start treatment prior to July 1st. The fact is, the majority of patients can be started August 1st and relatively few react when the season commences.

### Treatment During the Pollen Season

The advisability of treatment during the pollen season depends upon the time at which the patient comes for treatment. Since a period of two weeks is usually required for the development of a high grade of tolerance, it would seem needless to start a patient toward the end of the season—that is, during the last month of the season. However, at the beginning of the season or during the first month, treatment can be successfully carried out and relief given during the latter portion.

It is perhaps necessary to be more cautious with treatment during the season than with treatment given before the season commences because of the fact that the patient encounters and absorbs some of the pollen of the air. However, this is not great and is no ob-

stacle to successful treatment except for the fact that the patients frequenly have sneezing and running of the nose soon after the injection is given. This cannot be called evidence of a constitutional reaction, but rather a "focal reaction" analogous to that so frequently discussed concerning tuberculin therapy.

### Results of Pollen Therapy

No results are more irregular than those which follow pollen therapy unless treatment is adequately and carefully administered. In this case, the results obtained almost follow mathematical laws. In our earlier years when a one-tenth per cent (0.1 per cent) solution of pollen extract was the maximum strength used, practical relief was obtained in only about 40 per cent of cases. The following year, when the solutions used had a maximum strength of one per cent, practical relief was obtained in about 61 per cent of cases. A large proportion of the remainder, however, were relieved with intranasal treatments. Last season, when about ½ c.c. of a 5 per cent solution was used as a maximum dose, practical relief was obtained in almost every case and intranasal treatment was unnecessary.

It appears, on the whole, that patients with pollen disease are either easy to relieve or difficult to relieve. Of the former group, pollen therapy according to almost any plan seems to give partial or complete relief. This includes about 40 per cent of cases. In the remainder, however, treatment has to be given adequately and thoroughly if relief is to be obtained in a large proportion of cases. It has seemed impossible to predict either by history, duration of illness, or skin tests which cases will be easy to relieve and which will be difficult. One patient, for example, who gave a marked paternal and maternal history of the disease, who had had both hay fever and asthma since babyhood, and who gave intensely positive skin tests, was apparently permanently cured early in my experience with the disease by a very inadequate method of treatment given for two seasons.

Another patient who came to me at the beginning of a season with severe symptoms, gave intensely positive skin tests and was relieved completely for the entire season by the effect of the skin tests and one dose of pollen. Other cases, in whom the history and results of skin testing would seem to indicate a relatively fair case for treatment, have been more resistant. Many of these variances

are, of course, attributable to the habits and environment of the patient. If habits or business brings him in the vicinity of large ragweed patches on windy days, he will necessarily be difficult to relieve.

## Duration of Immunity

The duration of immunity gained through pollen therapy varies. This variance is great in localities which are overgrown with weeds of many different varieties and especially if the seasons are short. A patient who happens to be sensitive to a weed which is not common in this district is not intensely exposed. In this case, freedom from symptoms under treatment should last longer than for patients sensitive to common weeds to which they are intensely exposed.

One cannot rely upon the duration or immunity lasting more than six to eight weeks. However, it usually lasts longer than this. Relative immunity persists as a rule, to the second or third season. The best opportunity for determining the duration of complete immunity can be gained by physicians, such as Kahn and Watson, who can study the long Bermuda grass season—a season which lasts eight months or more and is relatively constant in its pollen production.

Patients treated for several seasons seem to have a more lasting and better immunity clinically than patients treated for one season only.

## Theoretical Basis for Pollen Therapy

When animals sensitized to horse serum are desensitized by Besredka's method, sensitiveness eventually returns. Presumably, they are resensitized by the serum used in desensitizing. Is this the result obtained in pollen therapy? It does not seem to me that this is true. I have never observed a patient who, during the second, third, or fourth season after treatment was worse than formerly unless the same could be accounted for by an unusual amount of pollen in the air—in fact, they have seemed the reverse in practically every instance. After all, theoretical immunity and practical clinical immunity are two totally different things so far as pollen sensitiveness is concerned and although skin sensitiveness returns after a thorough course in pollen therapy, this does not coincide with a return of clinical sensitiveness to the pollen as encountered naturally. Clinical sensitiveness may not return for months or years so that in a certain proportion of cases, such as Lowdermilk's personal experience, the cure seems permanent.

The theoretical basis for pollen treatment seems to me to amount practically to about the following.

Patients do not ordinarily react clinically to substances with which they come frequently into gross intimate contact. They react rather to substances which they meet with rarely or meet with in traces. In pollen treatment, we change this mode of contact from "occasional traces" to relatively gross intimate contact and this, I believe, gives our clinical result. Skin sensitivness is definitely reduced by treatment but this returns within a few weeks after treatment is discontinued. Clinical sensitiveness may or may not return coincident with this—in fact, as a rule, it does not return at the same time but later. It seems to me that relief does not depend entirely upon desensitization of the body tissues generally. This is no doubt a factor but there seems to be in addition to this another factor which gives rise to clinical tolerance, even though tissue sensitiveness returns. I would not venture to suggest a theoretical reason for this apparent tolerance except to say that it is apparently due to intimate gross contact.

## Summary of Results of Pollen Therapy

Whereas marked irregularities in the result of pollen therapy are interesting and rather frequent, they can be accounted for by differences in the degree of sensitiveness of the patient and by variance in the intensity of their exposure to pollen. It can be said in summarizing, that the more consistently the pollen treatment is given, the better the result is likely to be and that if a patient is treated thoroughly with potent pollen extract, a bad result should make one suspect an error in diagnosis.

## Specific Therapy with Proteins Other Than Pollen

My experience in the specific treatment of hypersensitiveness with protein other than pollen is small as compared with pollen therapy and has been confined largely to therapy with milk and egg. It has been possible in the majority of cases of sensitiveness to substances other than pollen for the patient to avoid the substance responsible for illness. For this reason, specific therapy was not thought necessary. Furthermore, treatment with egg and milk has not been so successful on the whole as therapy with pollen extract. This is believed to be the case for a very good reason. Patients

who react to pollen are sensitive to the substance as encountered naturally by the patient and as it is used in therapy, while patients sensitive to a food may not be sensitive to the food as it is encountered naturally and as it is used in treatment but may be sensitive to a totally different substance, namely, a digestive product or a new product formed during the process of cooking. In these cases, subcutaneous treatment with extract as ordinarily prepared in a laboratory would seem theoretically illogical. Treatment by mouth with the food prepared in the way it is ordinarily eaten would seem to offer more hope of success. Whereas, in several instances I have treated patients with milk or egg subcutaneously and obtained relative tolerance, this result has not been the rule. In one patient sensitive to egg, a few drops of a very dilute solution of egg by mouth or hypodermically caused asthma after a period of several hours. Tolerance for egg given subcutaneously was increased to a point where he could stand without ill effect, a relatively large dose. It was never possible even after this, however, to increase the tolerance for egg by mouth to a point where he could take more than eight drops of a solution prepared by mixing one drop of whole egg with 250 c.c. of salt solution. Treatment in this case was carried out faithfully by the mother during a period of six months and ended in failure. In another case, tolerance for raw and boiled egg was increased to a point where relatively large amounts by mouth were tolerated. The trace of egg contained in a little cake or noodles, however, continued to cause reaction.

It may be well to recapitulate and say that in treating for food sensitiveness, it is advisable to use a food in the form in which it makes the patient ill. In the case of sensitiveness to cooked egg, an extract of cooked egg should be used. If cake causes illness, this should be used in treatment rather than raw or boiled egg.

Upon purely theoretical grounds it might be suggested that treatment in food cases should be continued indefinitely. For example, if tolerance for egg by mouth is obtained, it would seem logical for the patient to try to keep up his tolerance by eating eggs each day for a period of months or years.

Case 23.—*Urticaria and Angioneurotic Edema Caused by Sugar.*—The patient, a girl, aged ten years, consulted Dr. W. F. Bowen of Topeka, Kansas, because of attacks of vomiting after the taking of food. Also because of hives and large swellings of the skin and mucous membranes. She was very ill, emaciated, and was running down at a rapid rate.

He found among other things that she was sensitive to sugar, even when taken in relatively pure state as crystallized rock candy. She was so sensitive that a very small amount taken by mouth would cause a reaction. She was sensitive not only to cane sugar, including rock candy, but also to beet sugar. She was not sensitive, however, to malt or to milk which contained milk sugar.

She was treated by feeding sugar by mouth, starting with one single granule and increasing a granule at a time until she could tolerate about seven granules at a dose. This amount actually caused illness at times. Her tolerance was gradually raised, however, to a point where she could stand ordinary amounts of sugar as encountered naturally and with this tolerance she gained rapidly in weight and health.

This case would seem analogous to honey sensitiveness which can usually be traced to the flower from which the honey is derived.

## Nonspecific Protein Treatment

In spite of one's like or dislike for the use of arbitrary remedies in the practice of medicine, it is in the present state of our knowledge advisable to use them at times. This may be said of nonspecific protein therapy in the treatment of allergy. Nonspecific protein therapy can occasionally be used with a fair temporary therapeutic result in the treatment of chronic asthma, chronic gastrointestinal disturbances, eczema, and other disorders (occurring as part of a general reaction) when no other more rational line of therapy presents itself. It is not recommended in the treatment of local reactions due to contact—such as hay fever or asthma caused by sensitiveness to air-borne substances, such as pollen or hair. In this type of case, the benefits, if any, do not justify the illness caused by the treatment. It is excusable, however, to try it in general cases when the primary source of the disorder cannot be found or removed.

It is not necessary to discuss nonspecific protein therapy broadly in this connection. Suffice it to say that it has an influence upon immunity and, under certain circumstances, has an influence upon the functional activity of organs supplied by the vegetative nervous system. The following case is cited to illustrate how marked this influence may be.

CASE 24.—*Showing the Effect of Nonspecific Vaccine Therapy upon Hyperperistalsis.*—The patient, a woman, aged thirty-five, had been for many months a victim of dyspepsia. The appendix and the gall bladder had been removed. The stomach and duodenal bulb had been found anatomically normal at operation. At the time she came to me she was complaining of pain in the epigastrium, worse after eating, and associated frequently with nausea and vomiting.

The pain was brought on by almost any type of food, especially if taken in more than very small amounts. She had at the same time, colon bacillus pyelitis and cystitis. The stomach upon fluoroscopic examination showed a high grade of spasticity and hyperperistalsis; in fact, in this respect, it exceeded any which I have examined. The picture was that of four or five large balls of barium which extended across the abdomen. During the treatment for pyelitis, she was given a small dose of autogenous colon bacillus vaccine subcutaneously. She had a profound reaction after this with chill, high fever and general malaise. She returned the following day to say that her stomach had been cured by the vaccine. It was examined again and was found to have changed from its previous condition of spasticity into a relaxed bag, which almost filled the abdomen. Peristaltic waves were hardly visible. Food no longer caused discomfort or nausea and the patient suffered no marked gastric disorder for months.

Without discussing the mechanism through which nonspecific protein therapy may exert its influence, suffice it to say that under certain conditions it has the practical effect of modifying the activity of certain organs supplied by the vagus and sympathetic nerves. Upon this basis I have used it occasionally as a remedy in the treatment of asthma, gastrointestinal disorders, dermatoses, and other general manifestations of reaction. The following case is cited as an example of the effect it can have in asthma.

Case 25.—*Severe Asthma Relieved Temporarily by Nonspecific Vaccine Therapy.*—The patient, a woman, aged fifty years, was brought into my office by the police with the statement that she had fallen unconscious on the street and was thought to be in a dying condition. She proved to have a very severe case of asthma of unknown origin and of long standing. She was given palliative remedies with a little temporary relief. She was later given 10,000,000 colon bacilli intravenously. A reaction followed with chill, high fever, malaise, and other symptoms. At the height of the reaction the bronchial spasm relaxed and she was able to breathe freely for the first time in weeks. She remained nearly free of symptoms for about two months when asthma recurred. It seems quite possible that hers was a heat sensitive case and that relief was a result of temperature elevation (see Part II).

I have chosen colon bacilli for use in nonspecific protein therapy because patients are almost always sensitive to colon bacilli and it seems to be the reaction which does good. Colon bacillus injected intracutaneously almost always gives rise to a marked local inflammatory reaction (not a hive reaction) within twenty-four hours in normal individuals. If injected subcutaneously or intravenously in small doses, it almost always gives a marked febrile reaction. As a rule, subcutaneous treatment is safer, less severe and is preferable.

If this fails, a smaller dose, roughly one-fifth to one-tenth the subcutaneous dose, can be used intravenously.

In view of the fact that patients with asthma and urticaria caused by sensitiveness to heat (to be described subsequently) frequently have markedly subnormal temperatures (94° to 97°) and react most violently when the temperature is lowest, we may well ask ourselves whether or not the effect of nonspecific protein therapy in asthma and urticaria is not frequently an indirect one effecting a temporary cure largely through keeping body temperature at a higher level.

**Summary of Nonspecific Protein Therapy.**—Through the use of colon bacilli subcutaneously or intravenously in very small doses, nonspecific protein therapy can be recommended in the treatment of general reactions if the more logical methods cannot be used for any reason or fail. Good results, if obtained, are rarely permanent. It apparently does little or no good in contact reactions and is not recommended for this.

## Symptomatic Treatment

I do not wish in this book to discuss at length the symptomatic treatment of allergy except with drugs, the effect of which seem relatively definite. The great majority of drugs which have been enthusiastically recommended by one physician or another as cures for a majority of cases, have proved in my experience to be either ineffective or variable in their effect. Possibly the results reported by different writers will be more harmonious when the different types of sensitiveness can be classified and the effect of the various remedial agents upon each carefully studied. It is certainly a fact that the results obtained with a given drug by physicians treating chiefly pollen cases will vary greatly from those of physicians treating chiefly perennial cases. For this reason, I do not feel that the time is opportune for the discussion of any agent except those which have a relatively consistent effect in certain types of cases.

**Adrenalin.**—Adrenalin is the one remedy which is relatively consistent in its effect upon all types of reaction. It is not only effective when applied locally, but as a rule, when given subcutaneously if the dose is properly adjusted. It appears to be effective in all types of cases when applied locally. It is effective in the great majority of cases when given subcutaneously, although

in some types more than in others. It is less effective apparently in contact cases than in general cases—that is, less in pollen hay fever, occurring as a local reaction, than in asthma occurring as part of a general reaction.

If one wishes the greatest benefit from adrenalin with its disagreeable effects at a minimum, it must be administered in the smallest dose which has the desired clinical effect. This varies in different individuals and varies in the same individual at different times.

It is not uncommon in chronic asthma to find that a patient can be relieved by fifteen drops of adrenalin by mouth, or by one or two minims subcutaneously each twenty-four hours. The same individual may require at other times several one c.c. doses during twenty-four hours, and adrenalin by mouth may be ineffective. I observed two patients who for months could keep themselves symptom free by the subcutaneous use of a few drops of adrenalin each day. During exacerbations in their illness, they suddenly became tolerant of its effect and required as much as four ounces each twenty-four hours to obtain noteworthy relief. Whereas at times the effect of two minims would give practical relief and tremor, at other times one c.c. or two c.c. doses would give little relief and this would often last not more than five minutes. Furthermore, during such intervals, adrenalin would fail to cause tremor. I cannot say that I approve of the use of enormous doses such as the above, but the patients were treated under the care of other physicians who were fearful of losing their cases if adrenalin were not repeatedly used in the doses mentioned. Strange to say, one or two minims of adrenalin subcutaneously will at times give pallor, and slight adrenalin tremor, while at other times when large doses are required for relief, pallor and tremor do not appear at all. During such periods of tolerance, it would seem advisable to support the adrenalin treatment with some other form of therapy and it is here, if ever, that the use of habit-forming drugs might be indicated temporarily. I have even used morphine, chloroform, and ether to meet such emergencies but do not approve of the use of either except to meet an emergency.

When a case of asthma is first seen and adrenalin is to be used, it is a good rule to give ½ c.c. of a 1:1000 solution subcutaneously at five-minute intervals until relief is obtained, or until tremor appears. Relief, as a rule, follows the tremor. One can estimate

with relative accuracy the size of the dose which will be required for recurrences. As a rule when symptoms return, or better still, if the attack can be anticipated by some sensation recognized by the patient, the dose as a rule can be reduced and upon subsequent recurrences, can be still further reduced. Frequently when several cubic centimeters are required to stop an original attack, a few minims will suffice to prevent subsequent attacks. This is especially true if the patient learns to administer adrenalin himself, and anticipates attacks by a few moments. When this point is reached, 15 minims of adrenalin in a half glass of water by mouth will often accomplish as good a result as the smaller dose subcutaneously.

Adrenalin should be given slowly; in fact, if a 2 c.c. dose is required, several minutes should be used, if possible, in its administration. This has been especially urged by Kahn who has been one of the strongest advocates of the free use of adrenalin in the treatment of asthma. It should be given intravenously only under desperate circumstances.

Adrenalin can be used apparently for weeks or months without apparent ill effect, although perhaps more experience is needed before the harmlessness of this drug can be relied upon if used for indefinite periods of time. I have observed several cases in which it has been used for months and years with no apparent ill effect. In one case, pigmented spots resembling large freckles became pronounced in several localities.

While adrenalin can apparently be used continuously for months without ill effect, it is best adapted for emergencies, and for temporary treatment, and should be discontinued as soon as measures which have a more lasting effect can be instituted.

**Pituitrin** applied locally causes mucous membranes to blanch and shrink just as adrenalin does. This effect is not quite so prompt, but lasts longer. If given subcutaneously it frequently has somewhat the same effect as adrenalin. As a rule, however, the result is less marked and less constant. If the drug is effective, however, it frequently gives a longer period of relief than adrenalin. In one case, adrenalin and pituitrin together were used to advantage. Koessler warns against the use of pituitrin on account of the frequency with which it contains histamine as an impurity.

**Atropine.**—Drugs of the atropine series are time-honored remedies in the treatment of asthma. Meltzer suggested its use in the

treatment of anaphylaxis. Atropine is effective in some cases even when given in small doses. In others it is ineffective. It can be used either locally or subcutaneously or by inhalation. If given by mouth or subcutaneously it should be pushed to the point of causing dryness of the mouth. It is rarely advisable to push the drug to the point of blurring vision. Some patients can tolerate $1/100$ grain two or three times daily, while others who are more susceptible cannot tolerate this amount. Atropine can frequently be used to advantage in conjunction with adrenalin. Often the appropriate use of atropine in small doses marks the difference between success and failure in the relief of patients who have been treated according to other principles outlined in the book. A patient nearly relieved by other means may often be completely relieved with the help of atropine.

**Acids.**—Dilute solutions of acid applied locally to the conjunctivae will frequently give symptomatic relief in ocular reactions according to Dr. W. E. Schutz. He advises this as an aid in the treatment of ocular and nasal reaction. The following prescription I have found very useful.

| | |
|---|---|
| Adrenalin 1-1000 | 1. |
| Dilute acetic acid | 0.3 |
| Resorcin 2% q.s. | 32. |

Sig: Apply locally when needed.

Acid inhalations give temporary relief in a limited number of cases as do acid applications to the skin in certain dermatoses. In treatment of the latter condition, soap should be avoided and the acid used should be very dilute (15 drops of dilute acetic acid to a glass of water).

**Thyroid Extract.**—Thyroid extract is beneficial in certain cases. It is apparently in those who have dysthyroid symptoms or subnormal temperature (see Part II). The effect of thyroid extract, however, is not constant.

**Insulin.**—Insulin was used in several cases that ran markedly subnormal temperatures in the hope of promoting metabolism and in this way keeping temperature at a higher level. In several cases it proved temporarily beneficial.

**Iodides.**—Potassium iodide is a time-honored drug used in the treatment of asthma. Its effect, however, is very irregular and it is difficult to state which type of case is likely to be relieved by it.

**Salicylates.**—Salicylates such as acetyl salicylate have a sphere of usefulness in the treatment of asthma. It should be given in doses of ten grains every three to four hours throughout the night as well as the day.

**Habit-Forming Drugs.**—Two drugs which are very effective in the treatment of asthma are unfortunately habit-forming and should rarely be used; namely, drugs of the cocaine series and drugs of the morphine series. Emergencies which justify their use rarely occur, and the dangers of producing morphinism by the use of this drug in chronic cases is great. It should only be used in desperate emergencies.

**Anesthetics.**—Anesthetics such as chloroform, ether, alcohol have a sphere of usefulness in desperate cases. They should only be used, however, temporarily and sparingly as an emergency measure and with great caution.

**Summary.**—To summarize, it can be said that adrenalin and atropine should be looked upon as the most useful symptomatic remedies, best adapted, however, for temporary use while more lasting methods are being instituted, and as an aid in treatment by other more lasting methods.

## General Summary

The numerous manifestations of allergy, such as hay fever, asthma, the dermatoses, the gastrointestinal, urological, and neurological symptoms, urticaria, angioneurotic edema, hypotension, etc., can be treated along five different lines; namely, avoidance or removal of the specific cause of illness, avoidance or removal of contributory causes, specific protein treatment, nonspecific protein treatment, and symptomatic treatment.

Avoidance or removal of the specific cause is the method of choice when this can be used.

Specific protein treatment is the method of choice when the specific cause of illness is known, but cannot be conveniently avoided, namely, in the case of sensitiveness to the common fall pollens or wool or to cooked egg, milk, or wheat.

When the specific cause of illness is not known, cannot be removed or treated specifically, nonspecific protein treatment is worthy of trial. This can be accomplished best, I believe, through the use of colon bacilli subcutaneously or in the very small doses intravenously.

Adrenalin and atropine are the most consistently useful symptomatic remedies and are well adapted for emergency use and for temporary use while the most lasting methods of treatment are being instituted.

The results of pollen therapy in the treatment of pollen hay fever and asthma are good. A poor result should make one suspect an error in diagnosis. The best results are obtained through the use of pollen extract subcutaneously by the short interval method. The maximum dose has to be large enough to give the patient a degree of tolerance great enough to enable him to tolerate the quantity of pollen with which he comes in contact. In Kansas City, this amounts to about 0.5 c.c. of a 5 per cent solution. In rural districts, the maximum dose required may be greater and in larger cities where the pollen content of the air is less, the maximum dose may be smaller. If pollen therapy is adequately and scientifically administered, relief can be obtained in practically every case.

Food cases can often be successfully treated by avoidance of cause and by the oral administration of the offending food in graduated doses.

# PART II

# REACTIONS CAUSED SPECIFICALLY BY ACTION OF PHYSICAL AGENTS, SUCH AS LIGHT, HEAT, COLD, MECHANICAL IRRITATION, FREEZING, AND BURNS, AND IN THE CASE OF HEAT SENSITIVENESS, INDIRECTLY BY THE EFFECT OF MENTAL OR PHYSICAL EFFORT

## CHAPTER XVII

## PHYSICAL ALLERGY—INTRODUCTION

In the previous chapters, several varieties of altered reaction have been described, each caused by sensitiveness to material substances. In the subsequent chapters, I wish to describe altered reaction quite similar in character to the foregoing which is not caused by sensitiveness to material substances, but apparently by specific hypersensitiveness to the action of physical agents, such as light, heat, cold, and mechanical irritants. In allergy of this type, we find several different varieties of reaction.

The use of the term "physical allergy" has been endorsed by Dr. H. Gideon Wells, who is well acquainted with the subject which will be discussed. I also discussed the term with Dr. Karl K. Koessler, who approved of it, and with Dr. A. F. Coca, who disapproved because of the indefiniteness of the term "allergy." He preferred the term "hypersensitiveness." The term "hypersensitiveness" is more expressive and more definite and would be preferable were it not for the fact that it is hard to use. Wells stated that the term "allergy" means nothing more than altered reaction and that it need not commit one to a view more detailed than this. It seems, furthermore, that the adjective "physical" should serve to separate this type of allergy from altered reaction caused by sensitiveness to material substances and that in using it I do not necessarily assume that the two conditions have been proved to be related.

In papers published previously, I described a case of urticaria caused specifically and solely by the action of light; in fact, solely by rays of light at the violet end of the spectrum. Also, a case identical to this in every respect except for the fact that the urticarial rash was caused solely and specifically by the action of cold; in fact, best by cold between the temperatures of 5 and 15° C. In each case, the reaction was similar to that observed in a number of cases of dermographia in which an urticarial rash could be brought out specifically and solely by mechanical irritation of the skin. I also described a case of a different nature in which a generalized

urticarial rash was brought out specifically and solely by the action of heat; in fact, by heat of any source, including that produced by the application of a hot compress to the skin, the drinking of hot water, the application of a diathermic current, and even by the heat generated by a little exercise, or emotional disturbance. It was estimated that during certain periods when the patient was unusually sensitive, the generation of one calorie of heat by exercise would cause the rash if the patient were heavily clad. The reaction could be prevented or stopped immediately by the application of cold of any source, such as by exposure of the skin to cold air, or to cold water or ice, by the drinking of cold water, or by the removal of clothing.

At the time that these cases were studied, I thought they were examples of the rarest illnesses. One year's search for cases of a similar nature, however, has convinced me that patients who react to, and are made ill by the action of a physical agent should be an everyday finding in a busy physician's office. During a period of one year, I have observed in excess of fifty cases. It is upon a careful study of thirty-seven of these that the following paragraphs are based.

It was very apparent at the outset of this study that reactions caused by physical agents fell into two distinct classes: First, those in which the reaction was confined to the area directly exposed to the physical agent, and second, those in which the reaction was widespread, and involved not only areas directly exposed but distant structures as well. The former type will be spoken of subsequently as "contact reactions," the latter as "reflex-like reactions."

It also became apparent after short study that the skin was not the commonest site of reaction in patients sensitive to physical agents, but that the nasal and bronchial mucous membrane reacted more frequently. I was finally surprised in finding that a large proportion of patients with asthma, "allergic coryza," erythema, pruritus, urticaria, angioneurotic edema, eczema, and even allergic shock, are actually sensitive specifically and solely to the action of a physical agent, such as light, heat, cold, or mechanical irritation, and in the case of heat sensitiveness, indirectly to the action of mental or physical exertion, and that such patients react invariably with allergic symptoms whenever they are suitably exposed to the physical agent to which they react. I am fully convinced now

that this type of sensitiveness is a relatively common cause of nasal, bronchial, and cutaneous reaction, ordinarily classed as "allergy," especially among the class of cases that gives negative tests to material agents, such as pollen, epithelium, or food.

The effect upon hive and asthma cases of changes in temperature and moisture in the air, "changes in barometric pressure," of heat, exercise, emotional disturbances and reflexes, has been noticed and mentioned to me by many patients. The effect of these agencies has been repeatedly mentioned in medical literature. This action, however, has been looked upon as a matter of secondary importance, and has been believed to be an inciting cause of reaction due primarily to some other fundamental process. In cases in which the illness has been directly attributed to the action of physical agents, no serious effort has been made to prove it to be allergic in origin. It is interesting in this connection to quote Bostock, who in 1819 described his own case of summer hay fever under the term "catarrhus aestivus." He believed the cause of his illness was heat and the sun's rays, and stated "by using every means of obtaining fresh air without much exertion, and by carefully avoiding a moist and close atmosphere, the symptoms may in some measure be kept off." He stated also, "during the last summer the patient was so situated as to be able to avoid almost every degree of bodily exertion; he remained nearly confined to the house for about six weeks, and the result was that, notwithstanding the unusual warmth of the season, he experienced much less of the affection than he had done for several years before." It is interesting to repeat that "he was relieved by using every means of obtaining fresh air," a procedure which makes pollen cases worse but which relieves heat sensitive cases such as I shall describe subsequently. His case harmonizes exactly with a case of urticaria caused by heat to be described under the term "Urticaria Calorica" with the exception of the fact that the skin was involved instead of the nasal mucous membrane.

For the last nine months, patients presenting symptoms such as hay fever, asthma, urticaria, angioneurotic edema, and eczema have been tested not only for specific sensitiveness to material substances, such as pollen, epithelium, and food, including intracutaneous tests with some 300 foreign substances, but have also been systematically tested with physical agents, such as ice applied to

the skin generally and locally, cold baths, refrigerated air at 37° F. and at 20° F., by hot applications, hot baths, dry heated air, moist heated air, and heat applied through the use of an autocondensation current, with sunlight and actinic ray, with physical exercise, and with changes in air pressure. These tests were carried out both on pollen sensitive patients and on patients who were apparently insensitive to material substances and were accomplished through the cooperation of Mr. Fred Wolferman of the Wolferman Grocery Company, Mr. H. Wartel of the Oak Street Baths, and Dr. O. J. Cunningham, who, by means of a large tank, can expose patients to different degrees of air pressure analogous to increases in barometric pressure.

Through this study I have been forced to look upon allergy from a totally different point of view than formerly and believe now that many of the so-called "nonsensitive cases" must be classed as a fifth type of allergy, namely, physical allergy, and that in this type there are several different varieties of reaction.

It is very apparent to me now that sensitiveness to the action of physical agents is a much broader subject than I first would believe—in fact, too broad for complete discussion in this volume. Reaction of the cutaneous tissues (which can be more accurately observed than reaction of the deeper structures) may bear not only a resemblance to the erythematous, itching, edematous eruption characteristic of the reaction of pollen disease but also eruptions of an inflammatory character (such as chilblains) which resemble more the tuberculin type of reaction. If the skin and fascia can react in this way (chilblain reaction) because of sensitiveness to a physical agent, other tissues should do so as well. Consequently, physical allergy of an inflammatory character may prove an important cause of diseases which are looked upon as essentially inflammatory in origin. It is not possible for me at this time, to do more than mention this phase of the subject.

Furthermore, it was observed that patients with thermic sensitiveness, that is, sensitiveness to heat and cold (of the reflex-like type) or combined sensitiveness to heat and cold (to be discussed subsequently) were unusually prone to have febrile attacks commonly diagnosed "bronchopneumonia," "coryza," or "influenza" upon slight exposure to weather changes—in fact, I found it necessary to avoid exposure of my patients to extremes of heat or

cold in testing because of a liability to severe reactions resembling influenza. Many of the cases gave a history of as many as two or three severe febrile attacks each winter and I found it necessary on this account to caution them against accidental exposure to heat or cold. Such illnesses may have occurred as a result of mechanical obstruction in the respiratory passages. This mechanical source of disturbance no doubt exists in the case of nasal and bronchial reaction and no doubt predisposes to infection. However, the cause appears to me to be deeper than this—in fact, patients sensitive to the action of physical agents of the reflex-like type seem actually to be unstable immunologically and seem predisposed to acute infections upon slight weather changes. This view is not out of line with the time-honored phrase "caught cold," and with the fact that "pneumonia" is prevalent in the changeable weather during spring and fall. It is not possible in this volume to discuss this subject in detail—in fact, my study of this phase of the subject would not justify it at the present time.

Consequently, in the subsequent chapters, my discussion will be confined to the type of reaction which simulates in general character the inherited human idiosyncrasies commonly classed as pollen disease, food and drug idiosyncrasies.

# CHAPTER XVIII

# CONTACT REACTIONS CAUSED BY LIGHT, HEAT, COLD, AND MECHANICAL IRRITANTS

The word, "contact reaction," is used to designate a type of reaction which is closely confined to the surface tissues directly exposed to the irritating agent. When large skin areas are exposed, however, constitutional symptoms become manifest. The following reactions have been observed and studied:

Orbital reaction caused by light and by exposure of the face to cold air.

Nasal reaction caused by breathing of cold air.

Bronchial reaction caused by the breathing of cold air.

Skin reactions (erythema, pruritus, urticaria) caused by light, cold, mechanical irritation, and burns.

Eczema of the exposed parts caused by light and cold.

Severe abdominal pain caused by the ingestion of cold drinks or foods.

Eosinophilia caused by light, cold, and mechanical irritants.

Shock caused by light and cold.

The reactions above mentioned were most definite and could easily be traced to the specific action of a physical agent. Reaction was caused by one agent only, except in the case of urticarial dermographia, in each of five cases of which, reaction was caused both by mechanical irritants and by freezing of the skin with ethyl chloride. Reactions were immediate in all the cases studied except three. In two of these caused by light and in one caused by mechanical irritation of the skin, the reaction was delayed for several hours or more.

## Contact Reactions Caused by Light

Normal individuals are benefited by the action of light if the exposure is suitable,—in fact, they are affected in different ways by light of different wave lengths. Patients with certain illnesses, such as rickets and tuberculosis, improve under the influence of

certain rays of light. Normal persons are made ill by the action of light if the exposure is great enough. The local effect of a long exposure of the normal skin is an inflammatory reaction and if the skin area exposed is large enough, constitutional symptoms, such as fever, malaise, and toxemia become manifest. Under pathologic conditions, patients may be unusually sensitive to light so that ordinary exposures give rise to skin lesions, such as hydroa vacciniforme, xeroderma pigmentosum, or eczema. Such examples of sensitiveness to light are well known in medical literature and have been studied experimentally by several observers, such as Pfeiffer, Betz, and others and attributed to the presence in the blood or tissues of photodynamic substances, such as hematoporphyrin. Their views are worthy of credence and a brief review. However, it is not with this type of reaction that I wish to deal in this book.

It was discovered accidentally by Raab that many fluorescent substances, such as eosin, fluorescein, and hematoporphyrin, are photodynamic; that is, under the influence of light, they possess certain remarkable qualities that they do not possess in the absence of light. Photodynamic substances, harmless in the absence of light, may be highly toxic to human beings or animals under the influence of light, can destroy bacteria or protozoa, modify the activity of enzymes, or even alter the structure and reactions of proteins. As an interesting illustration of the latter action, Dr. W. H. Howell reports that a solution of fibrinogen, if mixed with eosin or hematoporphyrin and exposed to the light, becomes incoagulable with heat at 90° C., and incapable of forming fibrin, after the addition of thrombin to the solution.

Interesting in this connection is a report by Betz, who, in studying hydroa vacciniforme, sensitized himself to light by the intravenous injection of 0.2 gm. of hematoporphyrin. Immediately afterward he found himself so sensitive to light that he dared not expose himself to direct sunlight for more than a few moments at a time. Shortly after the injection, typical absorption bands of hematoporphyrin were found on spectroscopic examination of the blood serum and urine. Hematoporphyrin disappeared from the blood serum and urine after a few days, so that, to account for his sensitiveness to light, which persisted for several months longer, he assumed that a portion had remained in the tissues.

Immediately after the injection, Betz exposed a small area on

his arm to the Finsen ray. A marked reaction followed shortly, which ended eventually in a deep ulcer, which healed slowly and produced a scar. This reaction he thought analogous to the eruption of hydroa vacciniforme. Shortly afterward he exposed his face to sunlight, with the result that an itching, edematous eruption appeared which almost obliterated his features, and did not subside for several hours. For several months after this, exposure of his skin to sunlight invariably caused edema and itching, the duration of which varied according to the length of exposure to light. His sensitiveness to light disappeared during the winter, several months after he had given himself the injection.

The type of case that I reported, although very rare, is not unknown in medical literature, and on account of the striking peculiarity of the illness, I do not doubt is described in the very early literature. The earliest description which I found, however, is that of Ward, who, in 1905, reported the case of a patient who, during a period of four years, became increasingly sensitive to sunlight and whose skin reacted with the formation of itching hives similar to my case, even in the detail that she was sensitive only to rays at the violet end of the spectrum. A similar case was reported by Ochs, in 1910.

My patient became sensitive to light without apparent cause; but the case seemed similar in many other respects to that of Betz, produced artificially with hematoporphyrin, and resembled closely the urticarial reaction of allergic individuals occurring as a result of contact with substances to which they are hypersensitive. In view of Betz's report, one might object to this illness being considered allergic in origin, for in his case hypersensitiveness to light appeared in an apparently normal man immediately after treatment with hematoporphyrin.

A study of my case yielded the following results:

CASE 26.—*Urticaria Solaris.*—*History.*—A woman, aged forty-three, married, had always been robust and well until four years before I saw her, when she noticed that she was sensitive to sunlight. This condition became worse each year until now she cannot stand one minute's exposure to summer sunlight without paying a penalty.

Two of seven brother and sisters of the patient are subject to seasonal hay fever. Several nieces and nephews are subject to hives, to the patient's knowledge. The family history is otherwise of no interest. The father died when the patient was young, and the mother had no marked evidence of allergy so

far as the patient knows. The past history is negative except for scarlet fever as a child, and slight arthritis. About the time of onset of the patient's illness, her face, neck, and arms were exposed to sunlight for several minutes when she was swimming. Severe itching, redness and edema of the exposed parts caused her to seek shade as quickly as possible. The swelling persisted through the night and through the following day, and was associated with chilly sensations,

Fig. 70.—Urticaria solaris: Large area of itching edema which appeared in five and one-half minutes after exposure of the skin to sunlight for two and one-half minutes. The irregularities in the figure were due to a shadow cast by the hands holding three pieces of square colored glass in contact with the skin. The shape of the shadow cast by the hands was modified slightly by the artist to illustrate better how closely the edema followed the outlines of the colored glass. The edema did not spread beyond the area exposed to light. Sensitiveness in this patient increased at a later date, so that a thirty second exposure sufficed to produce reaction. General symptoms were felt when large areas of skin were exposed. After subsidence of the reaction, further exposure of the area to light on the same day produced less or no reaction. Frequent exposure of an area gave rise to local tolerance for light, which lasted several days.

marked weakness, and malaise. After she remained in the house forty-eight hours, the skin became natural again in every respect, and she felt well. She had a similar experience later after exposure to sunlight for a few minutes when clad in white. For the last two years she has protected herself with the greatest care from light, wearing black gloves and a heavy black veil whenever she goes out of the house. In spite of this care, some of the more thinly clad parts of her body are often sufficiently exposed to cause itching, redness and swelling, which often persists for several hours. She has noticed that after the skin has been exposed and reacted to sunlight, further exposure on the same day causes less or little ill effect in the areas previously exposed. On one occasion, after exposure of the face to sunlight, she was momentarily blinded, and following this all objects appeared yellow for several minutes.

*Physical Examination* was negative except for a slight grade of obesity, a slightly enlarged thyroid gland, and bad tonsils.

*Laboratory Examinations.*—Urinalysis was negative. Neither the color nor the absorption spectrum of alkaline hematoporphyrin was found in the urine on several examinations.

Blood examinations were negative. The Wassermann reaction was negative. No hematoporphyrin was found in the serum on several examinations.

*Roentgen-ray Examinations* of the teeth, sinuses, and gastrointestinal tract were negative.

*Sensitization Tests.*—Intracutaneous tests with all the common meats, vegetables, dairy products, fruits, sea foods, nuts, condiments, grains, bacteria, pollen and extracts from animal hair and feathers were negative.

*Sensitization Tests with Physical Agents.*—The application of mechanical irritants (rubbing, scratching, and intracutaneous injections) and chemical irritants (even chloroform applied to the skin and covered with the hand until it caused pain) produced no perceptible effect on the skin.

*Sensitization Tests with Light.*—Exposure of the skin to sunlight over any area which was usually covered by clothing gave rise in two and one-half minutes to marked itching and erythema. This progressed without additional exposure to a typical itching hive covering the entire area exposed in five and one-half minutes. The redness and edema would appear with almost clock-like regularity if the time of exposure was sufficient (two and one-half minutes or more of afternoon sunlight during the month of March). The reaction differed from a hive only in the lack of a tendency to spread with pseudopod formation beyond the area directly exposed to the irritating agent. In this respect the reaction resembled urticarial dermographia to be described subsequently.

Exposure of the skin to the light of a 500 watt nitrogen lamp, carbon arc light, and mercury vapor quartz light, gave rise to a similar reaction, but more time was required. Sunlight filtered through colored glass, except violet glass, had no perceptible effect on the skin after ten minute exposures. Sunlight, filtered through violet or colorless glass, produced a hive in the same manner as the unfiltered light, except that a little more time was required. Exposure of the skin to heat, roentgen ray, and sunlight filtered through Wood's nickel oxide glass, produced no visible effect on the skin after exposures of from three to ten minutes.

An application of sunlight to the skin for two and one-half minutes produced a wheal which would disappear after one or two hours. Application of light to the skin for ten minutes produced a wheal which would not disappear sooner than from six to eight hours. The foregoing data applied to skin areas which were covered by clothing and for this reason were not ordinarily exposed to light. Exposure of the face and neck and arms and hands gave a little different reaction. Exposure of the forearm, for example, gave rise first to discrete hives which, on further exposure, would become confluent. Exposure of the face for one minute gave rise to a red, blotchy appearance which was very disagreeable to the patient and which was followed for forty-eight hours by small, painful spots. She did not allow us to repeat this experiment. I believe that a longer exposure would have given rise to a necrosing eruption.

*Eosinophilia.*—Skin reactions caused by light were immediately followed by an eosinophilia.

*Tolerance for Light.*—To determine whether or not tolerance for light could be increased by repeated exposure, several skin areas were exposed to light for varying periods of time on successive days. Light was applied over two areas in doses too small to have an effect on the skin; that is, for one minute and for two minute exposures on three successive days. This gave rise to slightly increased tolerance for light, so that on the fourth day an exposure of three minutes produced no perceptible effect on these particular areas. The skin surrounding them, however, was sensitive as before. The tolerance gained in this way was completely lost after several days, so that future exposure of two and one-half minutes gave rise to the usual reaction. Ten minute exposures on three successive days gave rise to erythema and a hive in each instance. The hive, however, was delayed in its time of appearance after the last exposure, and the reaction, on the whole, was much less intense and disappeared more quickly.

An area of skin on the left arm was exposed during a period of twenty-four days thirteen times, varying from five minutes to twenty-five minutes. The reaction became successively less intense. The erythema and itching appeared at the usual time, however, in two and one-half minutes. Discrete hives appeared even after the last exposure, but did not give rise to the same confluent area of brawny edema as was caused originally by an exposure of three minutes. They also disappeared much more quickly. The arm became slightly eczematous after these repeated treatments and for this reason the study was discontinued. After a period of two months, the tolerance thus gained was completely lost.

In view of the fact that exposure of the face for one minute gave rise to a painful reaction instead of the usual erythema, edema, and itching, and in view of the fact that repeated exposure of the arm did not give rise to more complete tolerance, it seemed rather a useless and possibly a harmful experiment to carry this study further. We were actually fearful that repeated long exposures might give rise to permanent lesions of the skin. We concluded that, although relative tolerance for sunlight could be obtained through repeated exposure to light, the tolerance gained in this way was not sufficient to be useful to the patient. Slight general tolerance of short duration followed the longer exposures. This was not marked enough, however, to be useful to the patient.

*Serum Studies.*—Defibrinated blood, untreated blood serum, and serum to which was added eosin, quinine, and methylene blue, were allowed to stand in the sun for periods of time varying from two hours to twenty-four hours. Each preparation was then injected intracutaneously into normal individuals, the patient, and patients with pollen allergy, with no noteworthy reaction resulting.

To the patient's serum, normal serum, and the serum of a patient with pollen allergy, and to solutions of pollen, horse dander, and egg albumen was added hematoporphyrin to a strength of 1:10,000. Each was allowed to stand in the sunlight for from one minute to twelve hours, and after different intervals of exposure, was injected intracutaneously into the patient, normal patients, and patients with pollen allergy. No noteworthy reaction was produced in normal individuals. Small, itching hives followed the injection of the treated serums (not the other proteins) in the patient. The degree of reaction was not constant. Small hives were obtained by similar injections into several but not all of the other allergy patients. They were not comparable in size, however, with reactions produced with other substances to which they were sensitive.

*Hematoporphyrin* in 1:1,000 dilution was injected intracutaneously into myself, two normal assistants, a number of patients with pollen allergy, and into the patient reported above. No noteworthy effect was observed in any instance except after the area injected was exposed to sunlight. In the case of normal subjects and pollen cases, an intermittent stinging sensation followed a two and one-half minute exposure, which became marked and disagreeable at the end of six minutes. In the case of the patient described above, no noteworthy reaction was observed until the skin was exposed to dim diffuse light. After an exposure of three minutes, a small hive (1 cm. in diameter) appeared at the site of injection. The surrounding skin was not affected by this exposure to light. This reaction, tried many times, was quite constant.

The foregoing two experiments—that is, the ones made by the intracutaneous injections of hematoporphyrin followed by exposure to diffuse light, and the intracutaneous injection of serum after treatment with hematoporphyrin and sunlight, were the only ones in which I succeeded in producing anything in the patient which resembled a hive except by exposure to light as described in the previous paragraphs. These reactions were not striking.

*Fluorescence.*—The patient was studied carefully for fluorescence by the use of light from a 500 watt nitrogen light filtered through a Wood's nickel oxide glass filter in a dark room. This filter allows the pentration only of near ultraviolet light, and makes most objects fluoresce. The crystalline lens, sclera, teeth, nails and skin of the patient were observed, and their fluorescence compared with the same tissues of normal subjects. Whereas there was some difference in fluorescence noted, the difference was not striking, and, in several instances, normal persons showed greater fluorescence than the patient.

The patient's blood serum and urine were also studied for fluorescence and compared with that of normal subjects. No constant noteworthy increase was observed. The fluorescence of the patient's serum was not nearly so great as normal serum to which was added a trace of hematoporphyrin, quinine, or eosin.

Exposure of the skin to sunlight under a glass slide pressed on the skin so

firmly as to render the skin almost bloodless gave about the same reaction as that produced in the uncompressed area surrounding the glass slide.

*Adrenalin.*—The subcutaneous injection of adrenalin in doses sufficient to produce a tremor did not prevent the usual reaction upon exposure to light.

It was concluded that, although the blood might possibly contain some photodynamic substance that could render it toxic, that this could not be demonstrated by means at our disposal. It seemed definite, however, that the chief source of the reaction resided in the tissues rather than in the blood.

This condition seems to be a clinical entity, and for it the name ''urticaria solaris'' is suggested.

**Summary of Case Report of Urticaria Solaris.**—The case here reported is interesting in that a woman with a family history of allergy spontaneously became so sensitive to light that upon exposure of the skin to the direct sunlight of a winter month for two and one-half minutes typical itching hives, associated with erythema of the skin, invariably appeared over the entire area exposed. The reaction differed from the urticaria of allergic individuals after contact with substances to which they are hypersensitive only in the fact that it had no tendency to spread with pseudopod formation beyond the area exposed to the irritating agent. This reaction was produced only by the blue violet rays of light.

Constitutional symptoms were felt on two occasions when a large area of skin was exposed to light.

A considerable degree of local skin tolerance was developed by repeated exposure of one area of the skin to light. A slight grade of general tolerance was noticed for a short time after these exposures. The tolerance gained in this way, however, was lost after a comparatively short time, so that this method of treatment did not appear a rational remedy for the condition.

Efforts to produce hives in this patient by agents other than direct exposure to light failed except in two instances, namely, by the intracutaneous injection of serum which had been treated with hematoporphyrin and exposed to sunlight, and by the intracutaneous injection of hematoporphyrin followed by exposure of the injected area to diffuse light for a short time. These reactions were slight and rather indefinite and were not comparable to those produced by two and one-half minute exposures to light.

### Discussion of Light Sensitiveness

Urticaria solaris seems analogous to urticaria dermographica and urticaria hiemalis, to be described subsequently, in that the reaction is almost entirely local and fails to spread beyond the area directly irritated. It should be classed, it seems to me, as a type of urticaria factitia and for it the name "urticaria solaris" is suggested. It will be noted that this type of reaction is quite different from the reflex-like type of reaction caused by light and other agents to be described in the subsequent chapter.

Light sensitive cases do not always give the same types of reaction as the one here described. Eczema of the exposed parts occurs not uncommonly as a result of the action of light. In three such cases studied by the writer, the patient gave a family and personal history of allergy, a physical examination and sensitization tests not materially different from that of the case just described. The reaction to light, however, differed in that several hours' exposure to the direct rays of sunlight were required for the production of reaction. Furthermore, the reaction was delayed, appearing not sooner than three to four hours after the beginning of the exposure. The greatest intensity of reaction was not reached for several additional hours when there would appear redness, itching of the skin, and a slight urticarial reaction. This was followed after about twenty-four hours by a scaley, weeping eczema of the skin which persisted for ten days or more. These are believed to represent cases of light sensitiveness of lesser degree but fundamentally the same in pathogenesis.

In two of the above cases the patient became tolerant of sunlight during the latter part of the summer months. This seemed, however, not to be real tolerance. It was attributed rather to the fact that a marked tanning of the skin which occurred after frequent exposure to light filtered out the blue rays. One of the patients would purposely tan herself on this account.

### Contact Reactions Caused by Cold

Normal individuals are beneficially affected by the action of cold if the exposure is suitable. The stimulating effect of the breathing of cold air, of the effect of cold air and cold water on the skin, and of the drinking of cold water is well known. Normal individuals

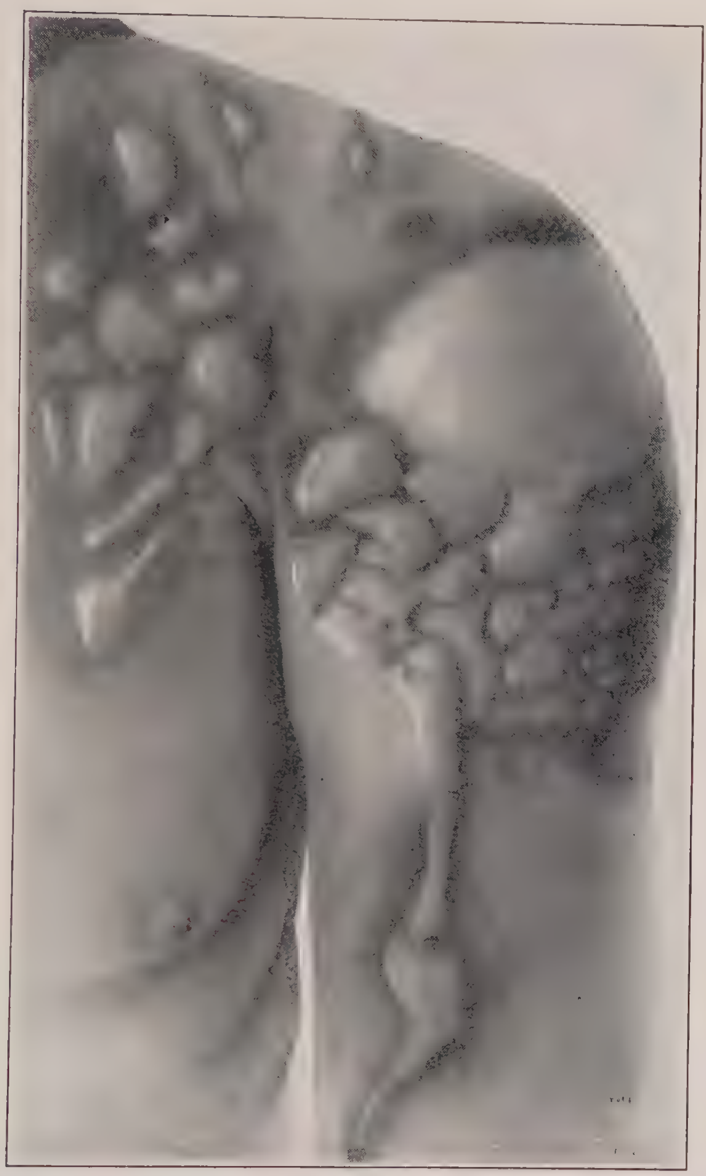

Fig. 71.—Urticaria hiemalis: Hives produced by the application of ice water for two minutes to the shoulder and chest. The hives on the shoulder eventually coalesced into one large hive. The hives on the chest each occupied the site of a large drop of water. The erythema shown appeared over areas moistened by the water. The urticarial edema did not spread beyond the wet areas. This is shown well in the area on the arm near the axilla, where the water ran down, covering the entire moist area. The "pseudopod" extending down the arm was caused by drops of cold water that ran down from the wet area. General symptoms were felt when a large skin area was exposed to cold. After subsidence of the reaction, the further application of cold water to the same area on the same day had no effect whatever. Local tolerance for cold followed frequent exposure of the skin to cold water, and lasted several days.

are made ill by the effect of cold if the exposure is great enough and react with local inflammation and constitutional symptoms.

Under pathologic conditions (chilblains and paroxysmal hemoglobinuria), a patient may be so sensitive to cold that relatively small exposures to cold cause illness. In a case reported by Ward, the patient was so sensitive to cold that exposure of her face for a few moments to a cold wind would result in blanching and stiffness of the skin as if frozen. Osler and also Fraser mention cases in which the patient invariably had urticaria if exposed to low temperature. In two cases which I observed the patients were excessively sensitive to cold, and invariably reacted locally with hives when sufficiently exposed.

CASE NO. 27.—*A Case of Urticaria Hiemalis*—A physician, aged forty, came to me complaining of hives. Two of his three children were troubled with urticaria. The patient had never been troubled with hives until about five months before consulting me, when he noticed that exposure of his face to a cold wind would cause swelling of the tongue, cheeks, eyelids and ears, with associated burning, itching, and redness of the skin, excessive lacrimation, itching of the eyes, sneezing and cough. The drinking of cold water caused pain in the mouth, throat, esophagus and stomach. On one occasion, when exposed more than usual to cold, he had a severe constitutional reaction which caused total collapse and required epinephrin for relief.

*Physical, Laboratory, and Roentgen-ray Examinations* were negative throughout or of no interest in this connection.

*Intracutaneous Tests* with a large variety of substances (more than 300) negative throughout.

*Tests with Physical Agents.*—Exposure of the skin to cold water for two minutes was followed by erythema and itching almost immediately, and by a hive at the end of five minutes. The reaction was brought out best by water at from 10° to 15° C. When ice was carefully applied so that presumably the temperature of the skin was brought to zero, practically no reaction occurred until the skin had warmed up, when the usual reaction would appear. Water at 20° C. caused very little reaction, and water at 30° C. none. Both erythema and hives would cover the entire wet area, but under no condition extended beyond the wet area. Freezing of the skin with ethyl chloride caused a hive, but not so promptly or so marked a reaction as was produced by cold water.

Efforts to produce hives by agents, such as light, heat, mechanical irritants, burns and chemical irritants, gave negative results.

*Eosinophilia.*—Exposure of a large area of the skin was followed by an eosinophilia (8 per cent).

*Epinephrin.*—The subcutaneous injection of epinephrin into the edematous area caused its immediate disappearance locally, but did not affect areas more than 1 or 2 cm. distant, nor did it markedly affect the reaction of the skin elsewhere on further application of cold.

*Local and General Tolerance for Cold.*—Skin areas that had reacted to water from 10° to 15° C. were totally exhausted by the reaction, so that further application of cold caused no effect whatever, neither erythema, itching, nor edema. The period of exhaustion lasted over two hours, but after twenty-four hours the skin reacted again about as usual.

A considerable degree of local skin tolerance was obtained by the application of cold to the same area of skin several times daily for several days. The tolerance produced in this way was of short duration. This observation is in harmony with the fact that the skin of the hands, face and forearms (more frequently exposed to cold than the skin of the body) had much more tolerance for cold than other skin areas.

Frequent exposure of large areas of skin gave rise to slight grade of general tolerance which lasted several days.

*Passive Transfer.*—Serum of the patient 0.01 c.c. was injected intracutaneously in several patients who were subject to pollen hay fever. After one hour and twenty-four hours the injected areas were exposed to cold water. No marked reaction followed. There was, however, a slight difference between the injected area and other skin areas after the exposure.

**Summary of a Case Report of Urticaria Hiemalis.**—The case above reported is that of a man who had two children troubled with urticaria but who himself had never had symptoms of allergy until some five months ago when he noticed itching and swelling of the face upon exposure to a cold wind, associated with swelling of the cheeks, tongue, eyelids, and ears, excessive lacrimation, sneezing, and cough. He also had pain in the stomach, mouth, throat, and esophagus upon the drinking of cold water and urticaria upon exposure of the skin to cold. The reaction was exactly similar to that described previously caused by exposure to light. The reaction, erythema, itching, and swelling would cover the entire area of skin exposed to cold and would not extend with pseudopod formation beyond this area. The reaction was brought out best by cold between the temperatures of 10° and 15° C., little reaction following exposure of the skin to ice temperature or to water at 20° C.

Reaction of the skin exhausted it locally so that further exposure of the exhausted area to cold produced less reaction. Reactivity of such areas would return within twenty-four hours. Frequent exposure of certain areas of skin to cold gave rise to local skin tolerance which would last for several days. Frequent exposure of larger areas of skin to cold gave rise to a transitory slightly increased general tolerance for cold.

The exposure of large areas of skin to cold were followed by shock and eosinophilia.

The skin reactions above mentioned were not prevented by ordinary doses of adrenalin administered subcutaneously.

Fig. 72.—Urticaria dermographica: Upper right, line of edema brought out by gentle scratching of the skin with a blunt piece of wood. Lower right, urticaria brought out by freezing with ethyl chlorid; this reaction was constant in four similar cases. Lower left, edema brought out by scratching with a glass slide. Exhaustion of skin follows a reaction of this sort, so that further mechanical irritation produces less or no effect.

An effort to transfer sensitiveness passively gave a negative or indefinite result.

This condition seemed similar to urticaria solaris in that the reactions were local and did not spread with pseudopod formation

beyond the exposed area. It should be classed as a type of urticaria factitia and for it the name "urticaria hiemalis" is suggested.

Since the study of this class was completed, another one similar in every detail has been observed.

Fig. 73.—Urticaria dermographica: Perfect image of a hand in relief brought out by slapping the skin gently in an extreme case of urticaria dermographica. The image was first outlined as an intense erythema, which appeared within fifteen seconds. The edema soon followed. Sensitive as this patient was, the hands and feet were totally unresponsive to mechanical irritation of any sort, showing the high grade of tolerance developed by frequent irritation even in a patient so sensitive as this.

### Reactions Caused by Mechanical Irritants

Normal persons are benefited by mechanical irritation of the skin, and gastrointestinal mucous membrane. In normal persons, marked mechanical irritation of the skin causes local inflammation. Under pathologic conditions, such as dermographia, slight irritation is

followed by marked erythema. Under certain other pathologic conditions, a scratch is followed by the formation of wheals. This condition has been called facticious urticaria. It seems analogous in every sense to the local types of urticaria just described caused by light and cold. The following case is reported as a classical example of this type of illness in severe grade.

CASE 28.—*Urticaria Dermographica.*—A boy, aged 8, whose father had been subject to asthma for a great many years, had been subject since infancy, to hives, which would invariably follow scratching of the skin. The history was otherwise negative or unimportant.

*Physical, Laboratory, and Roentgen-ray Examinations* were negative or of no interest in this connection.

*Intracutaneous Tests* with all the common foods, bacteria, and pollen, etc., gave negative reactions.

*Tests with Physical Agents.*—A slight scratch of the skin was followed within five seconds by a line of redness of the skin and slight itching, and within less than three minutes by a line of edema, which persisted for about forty-five minutes and then gradually disappeared. A wheal could be produced by any mechanical irritant, such as by scratching the skin with the nails or any relatively sharp instrument, by slapping or pinching the skin, or even by rubbing the skin with a piece of rough cotton gauze. The greater the irritation, the more prompt and marked the reaction.

Rubbing the skin with a soft woolen cloth or with a smooth object, such as a test tube or the side of a pencil, would cause no reaction whatever, even when the skin was rubbed until heat was produced by the friction.

Freezing of the skin with ethyl chloride would give rise to a wheal. The latter observation was also true in three similar cases in which the tests were made. It seems, therefore, to be a constant finding in this type of case.

Tests made with a great many other physical agents gave negative results. This included the application of cold water, the application of water at 50° C. for two minutes, water at 80° C. for fifteen seconds, chloroform liniment, ultraviolet light, the light and heat of a nitrogen lamp, high frequency current, positive and negative poles of a static current, and intracutaneous injections.

*General Reaction and Eosinophilia.*—A marked reaction produced over a large area of skin was followed by an eosinophilia (10 per cent on one occasion), redness of the face and ears, and slight generalized itching, which would lead to scratching and hives. This was interpreted as evidence of a slight general reaction.

*Local and General Tolerance for Mechanical Irritants.*—The skin was exhausted by a marked reaction. For example, an area that reacted after being scratched with a glass slide would not react again within a period of from one to two hours if again scratched with a glass slide. It would react, however, when scratched with a sharper instrument, such as a needle. The reaction produced in this way, however, was slight, and disappeared more quickly than a similar reaction produced at the same time over an untreated area. If an area of

skin was scratched several times with a glass slide, it would become totally inactive, so that not even a scratch with a sharp piece of wood would give rise to a wheal. An area that had reacted to freezing was partially exhausted to irritation by scratching, and vice versa. Exhaustion in neither case, however, was complete.

The skin of the hands and feet, which are naturally affected at frequent intervals by mechanical irritants, was highly resistant to the effect of scratching.

Frequent scratching of large areas of skin with a stiff brush gave rise to relative tolerance which would last several days. Reactions on such occasions would be associated with edema but not itching.

*Epinephrin.*—The administration of epinephrin (0.5 c.c. subcutaneously) did not prevent reactions.

**Summary of a Case Report of Urticaria Dermographica.**—The case above reported of urticaria dermographica is similar in family history, past history, and clinical findings to four others studied at the same time. The salient features are the following:

That a boy whose father had been subject to asthma, became spontaneously so sensitive to the effect of scratches on the skin that a hive reaction associated with marked erythema and itching came out under the influence of so little mechanical irritation that it appeared at times to occur almost spontaneously. The effect of mechanical irritants to the skin was invariably to produce a typical hive which would cover the entire area irritated but which would not spread with pseudopod formation beyond this area. Reaction of the skin exhausted it locally so that further application of the irritating agent was without apparent effect. A certain grade of local tolerance was produced by frequent irritation of a given area and a slight grade of general tolerance was produced by frequent scratching of large areas of skin at frequent intervals. The effect of this was to relieve the patient completely of the sensation of itching and reduce the amount of erythema. Edema, however, invariably appeared following scratches. The tolerance gained was only relative and was not lasting.

Mechanical irritation over large areas of skin gave rise to generalized itching and an eosinophilia.

The reaction was not prevented by adrenalin in dose of 0.5 c.c.

This condition has been described under the term urticaria factitia. It is evidently similar to the two conditions previously described, urticaria solaris and urticaria hiemalis, except in the circumstance that the reaction is brought out by scratches instead of by light or cold. It is suggested that the term urticaria factitia be

broadened to include all types of *local* urticaria brought out specifically by the action of physical agents and that the type here described caused by scratches be termed urticaria dermographica.

### Urticaria Ab Igne (Urticaria Caused by Burns)

This condition has not been studied so completely as the foregoing section because of lack of an opportunity for studying a case which reacted locally to ordinary grades of heat. The following case was hypersensitive to heat and reacted with localized urticaria when burned.

CASE 29.—*Urticaria Ab Igne.*—A married woman, aged thirty-four, with negative family history, since childhood had been subject to an erythematous, itching, edematous eruption whenever she was burned. Erythema and itching would develop gradually after about an hour locally at the site burned, and after from six to eight hours an itching hive would develop which would persist for about twelve hours. She frequently noticed wheals on her forearms and hands after cooking with frying grease, the little droplets of grease apparently sufficing to give rise to an eruption. On one occasion, when an area of skin 5 cm. in diameter was severely burned, she had a generalized urticarial rash.

*Physical and Laboratory Examinations* were negative.

*Tests with Heat.*—A test tube of hot water was applied to the skin at a temperature of 50° C. for thirty seconds, 60° C. for thirty seconds, 70° C. and 80° C. for fifteen seconds, and at 90° C. for one second. Within an hour there was slight redness around the 80° C. area. This was followed after a time by the appearance of a small blister and after about six hours by an elevated itching area of the skin which resembled a wheal.

The physical agents used in the study of the previous cases caused no unusual reaction.

Our study of this case, unfortunately, could not be completed. The history, however, seems clear enough to justify the use of the case in contrast to the reflex-like reaction caused by heat to be described under the title of "urticaria calorica."

### Description of Contact Reactions (A Type of Reaction)

The contact reactions heretofore described caused specifically and solely by a physical agent, such as light, cold, mechanical irritants, and burns, represent a distinct type of illness or rather, a distinct type of reaction, the characteristics of which are as follows:

*First.*—The patients almost invariably give a family history of hay fever, asthma, hives, or other manifestations of allergy (90 per cent of cases studied), but caused in other members of the family

by sensitiveness to pollen, dander or foods rather than by sensitiveness to physical agents.

*Second.*—The reaction is characterized by erythema, itching, and edema, which can be brought out specifically and solely by the action of a physical agent to which the patient is hypersensitive. In mild cases long exposures may cause dermatitis.

*Third.*—The hive reaction does not spread with pseudopod formation far beyond the area directly exposed to the irritating agent. The erythematous reaction, however, spreads indefinitely over irregular areas.

*Fourth.*—Sensitiveness appears usually prior to middle life.

*Fifth.*—The condition does not vary greatly in intensity from time to time.

*Sixth.*—The condition once established is permanent.

*Seventh.*—The skin can be exhausted locally by reaction so that further exposure of a given area of skin to the irritating agent on the same day has less or no effect. Reactivity of the skin usually returns after six to twenty-four hours.

*Eighth.*—Local tolerance follows frequent exposure of a given area of the skin. This result, however, is transitory and rarely lasts more than a few days.

*Ninth.*—Relative transitory general tolerance follows frequent exposure of large areas of skin.

*Tenth.*—Symptoms of general or constitutional reaction, such as collapse and eosinophilia, follow reaction of large areas of skin in the case of extreme sensitiveness to light and cold. Eosinophilia follows widespread reaction even in the scratch cases.

*Eleventh.*—Adrenalin in dosage sufficient to cause a tremor does not prevent or relieve the reaction completely.

*Twelfth—Passive Transfer of Hypersensitiveness.*—It would be interesting to know whether this type of sensitiveness can be transferred passively to normal individuals. Experiments for the purpose of determining this are unjustified except by the intracutaneous injection of the serum of sensitive individuals. In one case, however, of pernicious anemia in which an emergency transfusion had to be carried out, a large, plethoric donor was used who had urticaria dermographica in extreme grade. The recipient came from a nonallergic family and had never had symptoms of allergy herself. Immediately following a transfusion of one thousand c.c.

of blood and for several days afterwards, the recipient was tested carefully by scratching of the skin. She failed absolutely to respond with either a red or urticarial line. It seems justifiable from this one experiment to conclude that physical allergy of the contact type cannot be transferred readily to normal individuals who have no inherited predisposition to hypersensitiveness. The result might be the reverse, however, for recipients who inherit allergic tendencies.

The serum of a cold sensitive case was injected intracutaneously into several patients who were subject to pollen disease. Exposure of the injected areas to cold gave negative or indefinite results.

* * * * * * *

The type of reaction here described might be called, for the sake of emphasis, a contact reaction, and should be distinguished from diffuse or reflex-like reactions and from general or constitutional reactions which follow exposure of large areas of skin in the contact cases. It should be classified as a type of factitious urticaria, and under subheads can be included the illnesses "urticaria solaris," "urticaria hiemalis," "urticaria dermographica," "urticaria ab igne," etc.

Contact reaction can involve not only the skin, but also the mucous membrane, giving rise to marked local reactions. It may be repeated at this point that both cases of urticaria hiemalis had redness of the eyes, increased lacrimal secretion and sneezing when their faces were exposed to a cold wind, and pain in the abdomen after the drinking of cold water. The light sensitive case had temporary blindness on two occasions after exposure of the face to sunlight.

### Similarities between Contact Reactions and Pollen Reactions

It seems inadvisable at this time to insist that contact reactions caused by physical agents represent the same type of illness as pollen disease, although they are similar in almost every respect. For example, the family history is the same in each case; reactions occur locally at the site of application of the irritating agents in each case, and when the dose is sufficient, general reaction and eosinophilia are likely to ensue; tissues are exhausted locally by reaction in each instance so that further local application of the irritating agent is practically without effect; local tolerance follows

appropriate treatment with the offending agent in each case and general tolerance follows gross treatment with the irritating agent in each case. Finally, the reaction is not completely stopped by subcutaneous injections of ordinary doses (from 0.5 to 1 c.c.) of epinephrin.

Pollen reactions differ from the reactions caused by physical agents, however, in the fact that edema spreads with pseudopod formation far beyond the site of injection of pollen extract into the skin. This difference might be due, in part at least, to the fact that pollen solutions can spread through the lymph channels in the skin. Furthermore, the general tolerance produced by the treatment of pollen sensitive cases with pollen extract is greater than the tolerance which can be produced in physical cases by treatment. This difference with physical agents is due, possibly, to the fact that the dose which can be administered in pollen cases is much greater than that which can be administered satisfactorily in the physical cases through treatment with physical agents.

## Theoretical Explanation of Contact Reactions

What are the possible explanations of the remarkable phenomena observed? Several suggest themselves as worthy of consideration.

*First.*—The one explanation which seems to me to be most logical, is based on an assumption that patients with allergic tendencies might become specifically hypersensitive to some new body formed in the tissues solely under the influence of one specific physical agent, such as certain rays of light or heat or cold of certain specific grades, or possibly other analogous physical agencies. We know that heat, cold and light can each cause an aggregation of protein molecules and chemical changes in proteins *in vitro*. I am not wandering far from the realm of either fact or theory in assuming that this, under certain circumstances, takes place *in vivo*, and that some patients with allergic tendencies might actually become specifically hypersensitive to a new body formed in this way and react with hives just as they would upon suitable contact with pollen if they had happened to become sensitive to pollen. Since patients can become sensitive to and be made ill by the minute quantity of certain specific pollens in the air at certain seasons, they surely could become sensitive to and be made ill by some unusual

substance formed in the tissues under the influence of a physical agent.

*Second.*—An additional possibility must be mentioned and taken into consideration seriously. It was shown in 1910 by Barger and Dale, and in 1912 by Allan Eustis, that a protein split product, histamine, if injected subcutaneously into animals, produces bronchial constriction very similar to that found in animals dying in anaphylactic shock, and by Eustis that if applied to the skin of human beings in a 1 to 1,000 solution, gives rise to a local hive reaction. This finding has been verified by Koessler and others. It seems quite possible that in sensitive persons under certain circumstances, the action of a physical agent might break down certain protein molecules with the liberation of a histamine-like body, and that this could produce some of the clinical symptoms described in this paper. This view seems particularly applicable to contact reactions of the skin that are characterized, like histamine reactions, by the failure of pseudopods to extend out beyond the skin areas directly affected.

*Third.*—That through the action of some substance, possibly such as hematoporphyrin and light, or roentgen ray or actinic ray, the temperature at which certain organic bodies can jellify or tend to coagulate might have been so changed that aggregation of their molecules could be caused by the action of a physical agent, so that direct damage to certain tissue cells could be produced by them even in the amounts encountered under natural conditions.

It may be mentioned here that animals can be so sensitized to light by the intravenous injection of hematoporphyrin that a relatively short exposure to light results fatally; that paramesia caudatum can be so sensitized to heat through the action of the actinic ray, radium ray, or roentgen ray that a rise of temperature of a few degrees in their medium results fatally; that egg white can be coagulated at room temperature through the action of the actinic ray and by ordinary sunlight if hematoporphyrin is added to the solution; and, finally, that the temperature at which albumin coagulates and gelatin liquefies can be changed through the action of physical agents, such as the roentgen ray and actinic ray.

It seems not impossible, in view of these experiments, that an aggregation of protein molecules might occur intracellularly under the action of certain physical agents, and in this way give rise to

an insult to the cell which could cause a reaction locally and, in case of involvement of large areas of skin, could set free poisonous bodies which could give rise to general reaction and collapse. In view of the negative results obtained by the intracutaneous injection of the serums of my patients into normal individuals and hay fever patients followed by exposure of the injected areas to the action of the physical agents mentioned, one would be inclined to believe either that this view is untenable or that the substances responsible for the reaction in these cases reside in the tissue cells rather than in the plasma.

*Fourth.*—According to the experiments of Dr. Janet H. Clark, the various proteins of plasma, if separated from plasma and purified, can be coagulated by the action of the actinic ray. Plasma itself, however, cannot be coagulated in this way. According to her view, the plasma contains protective substances that hinder light rays from coagulating its protein. The existence of such substances would seem theoretically quite necessary for the protection of the surface protein, especially in animals that are exposed frequently to light. It seemed quite possible that sensitiveness to light might be accounted for through a lack of such protecting bodies, and that similar mechanisms might be involved in the patients sensitive to heat and cold. The serum of the light-sensitive patient was studied from this point of view, however, both by Dr. Clark and by me, and found to behave like normal serum on exposure to light.

*Fifth.*—We have in the normal body sense organs for the perception of each of the physical agents, light, heat, cold, and mechanical irritation, which caused the reactions described. No doubt, sense organs are provided with chemical bodies which transform physical energy of certain types into chemical energy. The chemical reaction set up gives rise, no doubt, to nerve impulses which are transmitted to the brain and recognized as having been caused by a certain physical agent. It seems conceivable that under pathologic conditions the chemical bodies which transform respectively light or heat or cold or mechanical irritation into chemical energy might escape from their confinement at the nerve terminals and might become generally distributed. If this were the case, each tissue cell which absorbed it should become sensitive to and capable of reacting to the influence of a specific physical agent in the same fashion as cells at the sensory nerve terminals. If such were the case, it

would seem likely that a physical agent might produce very damaging reactions in surface cells.

Whereas this view might seem fantastic, it is not out of line with conditions which we find in the body with other pathologic conditions. For example, bile is ordinarily confined to the liver cells and biliary tract. However, it is occasionally absorbed in great quantity from the liver, so most of the tissue cells in the body are stained by it. Under certain pathologic conditions, such as Melanotic sarcoma and Addison's disease, pigment is formed in great quantity and distributed through the body. It is not beyond the realm of theory that under certain circumstances, the sensory tissue cells might produce an abnormal quantity of the chemical body which makes them sensitive and that such might be absorbed by the blood and distributed generally throughout the body. If this were the case, many tissues which are not ordinarily affected by physical agents in ordinary amounts might become highly sensitive to their action.

## Symptoms

The symptoms in this type of reaction are confined almost entirely to the point of contact, although general symptoms resembling shock occur when the surface tissues involved are great enough.

The most striking symptoms are the cutaneous which, in their acute form, amount to redness, itching, and edema, not unlike the ordinary hive. In mild cases where prolonged exposure is required to produce reaction and in cases where repeated slight exposure gives rise to frequent slight reactions, structural changes in the skin may occur. In more marked cases this amounts to an eczematoid rash characterized by a thickening of the tissues, redness, desquamation, increased glandular secretion, associated with slight itching. Frequent repeated reactions occasionally give rise to telangiectases and to the occurrence of "solitary" reactions. The latter may appear as discrete hives in the more sensitive cases and as papules or papillary eczema in the cases of milder reaction of longer standing.

The ocular, nasal, and bronchial symptoms are not unlike those produced by pollen sensitiveness described under this heading in a previous chapter One additional ocular symptom, however, is

very evident in light sensitive cases, namely, photophobia. Even temporary blindness may follow marked exposure to light.

The abdominal symptoms amount to epigastric pain and dyspeptic symptoms which follow the ingestion of cold drinks or cold foods in cold sensitive cases.

## Diagnosis of Contact Reactions

The diagnosis of contact reactions caused by light, heat, cold, and mechanical irritation is simple if reactions are prompt and outspoken. As a rule, the patients themselves notice a relationship between cause and effect. An objective diagnosis can be made readily by exposing small areas of skin to sunlight, cold water, hot water, or mechanical irritation. If reaction appears within a few moments characterized by erythema, itching, and swelling, the diagnosis should be considered conclusive. Strange to say, patients sensitive to one of these agents do not often react locally to more than one, although patients subject to contact reaction occasionally are subject to reflex-like reactions caused by another physical agent. For example, one patient who had local eczema upon exposure to light, had asthma upon exposure of the skin to heat. One scratch case (urticarial dermographia) had asthma caused by the effect of cold upon the skin and was also sensitive to hair.

When reactions are delayed, symptoms appear, as a rule, only after more prolonged exposure and come out as eczema more often than as definite wheals. In this case, a relationship between cause and effect is often unnoticed by the patient. Furthermore, tests are difficult to carry out. In one case sensitive to scratches, wheals would not appear for several hours. In two cases sensitive to light, the reaction did not appear under the application of a dose of ultraviolet light which caused a blister. However, exposure for several hours to sunlight gave rise to a typical eczematoid eruption which appeared the following day. Eczematoid rashes confined to the exposed parts should always make one suspect sensitiveness to light or cold. Light should be suspected especially if the shaded areas of the skin are free.

## Treatment

Contact reactions caused by light and cold should be considered serious illnesses, especially if the reactions occur promptly. If

large areas of skin are exposed in either case, dangerous symptoms of shock may appear within a short time. Reactions of this sort should be treated with full doses of adrenalin subcutaneously.

**Light Sensitive Cases.**—The treatment in light sensitive cases depends upon adequate protection of the patient from light. The extent to which the patient should be protected varies with the degree of sensitiveness of the individual and varies in the same individual under different environments. Individuals who are mildly sensitive can tolerate winter sunlight but not summer sunlight. Furthermore, such individuals may tolerate summer sunlight in a moist climate but suffer severe reaction after short exposures in a dry climate. One patient who reacted to summer sunlight in Iowa was free of symptoms in winter even though frequently exposed to sunlight. She was unable, however, even during the winter months, to tolerate the sunlight in New Orleans. In moist climates, the damaging rays of light are filtered out to a large extent so that patients who are highly sensitive should be advised to seek localities such as the Northwest, because light sensitiveness once established seems permanent. Patients who are highly sensitive have to content themselves with indoor life on sunny days and should they be forced to go out, should wear dark clothing, a veil, and dark gloves. It is highly important to protect the eyes from exposure to sunlight since even short exposures may cause temporary blindness in highly sensitized cases. Long exposures might cause permanent damage to the retina. For this reason colored glasses should be used upon exposure to strong light. In mildly sensitive cases practical tolerance can be attained by the tanning of the skin.

Lotions and ointments often do more harm than good because of increasing the transparency of the skin. Pink or brown powders or fat-free casein colored pink or brown afford slight protection from the damaging rays of light and are useful in mildly sensitive cases.

**Cold Sensitive Cases.**—Cold sensitive cases would seek warm climates if this is feasible because the condition once established seems permanent. Above all, they should avoid occupations which subject them to exposure to cold moist air. One patient, a physician, upon three occasions had a reaction which he feared would terminate

fatally after accidental exposure to cold wet wind. Cold sensitive cases should avoid cold baths, cold drinks, and cold foods.

Relative tolerance can be obtained in cold sensitive cases by application of cold water to gradually increasing areas of skin surface. This, however, in two cases under my observations, did not appear to be a practical remedy. It might afford practical protection in mildly sensitive cases.

**Urticaria Dermographica.** This illness is disagreeable rather than dangerous. Several of my most sensitive cases were rendered miserable by itching hives whenever they were subjected to unusual rubbing by rough garments or from slight scratches made involuntarily. Patients of this sort are occasionally so sensitive that the eruption actually appears to occur almost spontaneously. These may be rendered relatively tolerant by frequent mechanical irritation of the skin generally with a stiff brush—in fact, in each case treated in this way the symptom itching was almost completely relieved within a few days. Although itching and redness were almost completely relieved, wheals continued to appear under the influence of scratches. In one patient whose blood pressure was constantly above 170, a reduction to normal followed this treatment taken over a period of about two weeks and he felt that his general health was improved.

# CHAPTER XIX

## REFLEX-LIKE REACTIONS CAUSED BY HEAT, COLD, AND LIGHT

Reflex-like reaction is a term used to designate reaction caused in tissues not directly exposed to the action of a physical agent. Reactions of this type may be confined to one locality or to one structure, such as the skin, nasal mucous membrane, or bronchial tree, or may be widespread, involving several or many different structures. The following reactions have been observed and studied.

*First.*—Orbital and nasal reactions caused by heat and cold and nasal reaction by the effect of light on the retina.

*Second.*—Bronchial reactions caused by heat and cold.

*Third.*—Skin reactions (erythema, pruritus, superficial urticaria) caused by heat and cold. Generalized scaly dermatitis caused by heat.

*Fourth.*—Deep urticaria and angioneurotic edema caused by heat and cold.

*Fifth.*—Severe abdominal pain caused by the ingestion of cold drinks or cold foods.

*Sixth.*—Diarrhea caused by the ingestion of hot drinks or foods.

*Seventh.*—Eosinophilia caused by heat and cold.

*Eighth.*—Shock caused by heat.

The paragraphs which follow are based upon a study of 27 patients who were subject to reflex-like reactions caused specifically by a physical agent. A few of these cases were also subject to contact reaction caused by a physical agent and a few were also sensitive to a material agent of some sort, such as pollen or dander or food. In two cases, the three types of sensitiveness were present simultaneously in the same individual. Twenty-five of the twenty-seven cases were sensitive to heat or cold or to the combined action of both. Two were subject to nasal reaction caused by the effect of light upon the retina.

It may be stated in advance that this subject cannot be discussed with the same degree of definiteness as were the contact reactions.

The condition is much more complex and furthermore, since tissues other than the skin were frequently involved, the reactions could not be observed so accurately. This type of reaction may seem complex. However, I do not believe, with the data at hand, that it is possible to make it seem simple. Furthermore, there are several gaps in the chain of data which will have to be filled in by later work.

Except for the cases of nasal reaction caused by the effect of light upon the retina, the reflex-like reactions studied were all due apparently to sensitiveness to heat or cold or to the combined effect of both. Heat sensitiveness was more common than cold sensitiveness but because of combined sensitiveness, the majority of heat sensitive patients reacted also upon exposure to cold. Thermic reactions, for the sake of convenience in description, may be divided into several types.

*First.*—Reactions caused by calories of heat regardless of their source or location.

*Second.*—Reactions caused by a local increase in temperature.

*Third.*—Reactions caused by cold regardless of its source or location.

*Fourth.*—Reactions caused by a local reduction in temperature.

*Fifth.*—Reaction caused by the simultaneous effect of cold in one locality and heat in another.

A number of combinations of the above types were observed which gave rise to very peculiar clinical pictures and to extremely misleading case histories. Many cases of combined sensitiveness, for example, gave a history of a reaction solely upon exposure to one of the agents, cold or heat, in spite of the fact that reaction was actually caused by the combined effect of the two. In several heat sensitive cases, the patient's complaint was that of reaction caused solely by exposure to cold. This can be accounted for in the majority of cases by the fact that reaction is caused much more often by a change in temperature than by a temperature of a certain specific grade—in other words, contrast between temperatures seems to be the controlling factor. For example, patients who react to heat frequently react to heat only after a previous exposure to cold and vice versa, cold sensitive cases react to cold only after previous exposure to heat. This, in several cases, gave rise to such misleading statements, as those of several heat sensitive patients who stated

with great positiveness that they reacted only in winter upon exposure to intense cold. In them, it was found upon testing that exposure to cold did not cause reaction, but that a rise in temperature (local or general) after exposure to cold would cause the reaction immediately. Not only was the above true, but in certain individuals tolerance for the agent to which they reacted developed apparently after exposure for several days so that symptoms were prone to occur chiefly with weather changes—that is, during the change from summer to fall or fall to winter or during the change from winter to spring or from spring to summer. Several cases give seasonal histories which would rank in its definiteness with that of pollen cases. An effort will be made to illustrate the abovementioned reactions through a description of several cases. It is believed, however, that few will understand the subject or accept it as a reality until after they have had actual experience with outspoken cases which react promptly.

## Heat Sensitiveness

Heat sensitiveness is apparently the commonest cause of physical allergy. It is characterized by reaction brought on specifically by the effect of heat. There are apparently several varieties of heat sensitiveness. One is characterized by reaction caused by calories of heat, regardless of their source. In a second variety reaction is caused by a local increase in temperature, such as nasal reaction caused by the application of a hot compress to the nose or by the breathing of warm moist air. In either variety, reaction is a result chiefly of change in temperature from cold to heat, that is, reaction caused by heat is augmented if the patient is previously exposed to cold. In a third type, we find combined sensitiveness—that is, reaction caused by the local action of heat on some structure, such as the nose or bronchial tubes, greatly accelerated and exaggerated by the simultaneous effect of cold upon some distant structure, such as the skin.

The difference between these groups of cases seems more apparent than real for in almost every case reaction seems to be caused more easily by a change in temperature or uneven distribution of heat than by a constant temperature of a given grade. While these groups of cases may be closely related pathologically, they are often grossly different clinically. They are, therefore, grouped informally as

above mentioned simply for the purpose of emphasizing clinical difference—not for the purpose of separating them definitely into different pathologic types.

**Heat Sensitiveness of the First Variety** is characterized by reaction caused by calories of heat of any source. This includes in excessively sensitive cases, even the slight amount of heat produced by mental or physical exertion when the patient is warmly clad. The heat produced by walking up a few steps, putting on an overcoat, or even by turning over quickly in bed or by an argument or by crying or laughing, is often sufficient to cause reaction. Such reactions can be stopped immediately or prevented by the simultaneous application of ice, cold water, or even cold air to the skin.

The following case is cited as a classical example of heat sensitiveness of this type. The patient was peculiarly adapted to a careful study because of the fact that his reactions were immediate and definite and because of the fact that the skin was involved and could be observed accurately.

CASE 30.—*Urticaria Calorica.*—A man, aged twenty-two, came to me complaining of an itching, burning eruption of the skin. The family and past history were negative. For two months before seeing me, he had been subject to generalized itching, burning and redness of the skin, usually associated with an urticarial rash whenever he was exposed to a little heat, when he exercised, or when he was subjected to mental excitement when in a warm room. The condition had been constantly present since its first appearance, but was worse at times than at others. On certain days he would break out frequently (often twenty-five times within twenty-four hours). He would usually react with a rash on entering a warm room, when covered up too warmly in bed, after the mild exercise of putting on a coat, after the slight mental excitement coincident with watching an athletic contest, or on becoming a little angry or vexed. An interesting business deal was usually interrupted by an attack of intense itching.

The itching rarely persisted more than five minutes. The urticarial rash, however, usually lasted longer, but rarely for more than thirty minutes, even when the patient remained at the same temperature.

The attack could always be cut short or prevented by the application of either cold air or cold water.

Constitutional symptoms, other than itching and the rash, had not been noticed.

Physical, laboratory and roentgen-ray examination, and intracutaneous tests were all negative.

The temperature taken over a considerable period of time was almost constantly subnormal, ranging from 96° F. in the morning to 97° or 98° in the afternoon. The usual temperature was about 97°. It was noticed that the reactions were more frequent and easier to bring out on the days when the patient's temperature started out low. On one day when the morning temperature was 99° on account of a cold, he had no attacks at all.

Following the application of hot water to the skin, the heat from a nitrogen lamp, or the heat from an autocondensation current or from a diathermic current, there would appear within a few seconds a generalized blotchy erythema of the skin associated with intense itching. This would be followed within one minute by the appearance of hives of varying size. When the attack was light, the hives were very small. With severe attacks, some measure 1 cm. in diameter.

On some days, attacks could be brought out by remarkably little heat—as little as thirty seconds' exposure of the forearm to the heat from a 1,000 watt nitrogen lamp at a distance of 5 cm. would suffice. Each attack was associated

Fig. 74.—Urticaria calorica. Urticaria caused by the action of heat. This generalized rash followed exposure of the right shoulder to the heat of a nitrogen lamp for one minute. On days when the patient was unusually sensitive, a rash would follow a fifteen second exposure, and some of the hives would be much larger. Reactions of the same sort could be brought out by physical or mental exertion. Each reaction was associated with a rise of temperature of 0.2° F. or more and could be stopped or prevented by the application of cold water to the skin. Five reactions of this sort were produced within a period of one hour, but could not be produced after the body temperature had been raised to normal by heat.

with an immediate rise of temperature of 0.2 degree or more. The temperature would often rise spontaneously, however, during the day without an outbreak of urticaria.

His attacks could be cut short or prevented by the local application of cold water or ice to the arms and hands. This, however, was not associated with any reduction in the body temperature.

Heat was applied to the right shoulder for three minutes, and simultaneously ice was rubbed on the chest and back. Neither rash nor itching appeared. On further application of heat for one minute without ice, the typical eruption occurred.

Slight exercise (bending over ten times) while clad would bring out the rash. Relatively severe exercise with the body exposed to cool air or while holding ice in the hands produced no such effect. The same phenomenon followed mental effort and could be prevented by the application of ice.

A rubber tourniquet was applied to the arm so tightly that blood could neither enter nor leave the arm (except through anastomoses with vessels in the bone marrow). The heat from a nitrogen lamp was applied to the forearm below the tourniquet for one minute. At the end of this time a generalized erythema and itching made its appearance, followed by the typical urticarial rash.

Exhaustion of reactivity to heat followed exposure to heat of such a degree as to cause not only a reaction, but also a marked rise in body temperature. Several reactions giving a rise of temperature to 98.4° would prevent further reaction on ordinary exposure to heat or after exercise or mental effort. Tolerance was given by anything which would prevent the unusually low morning temperature. This interesting fact is worthy of emphasis, for reactions were prevented even by an attack of acute tonsillitis while the temperature remained above normal.

Slight eosinophilia (10 per cent on one occasion) followed a severe reaction.

Visible perspiration was not noticed on any examination except once, after the administration of epinephrin.

The administration of epinephrin (0.5 c.c. subcutaneously) enabled the patient to tolerate without symptoms at least fifty times as much heat as caused a marked reaction previous to its administration.

He was unaffected by light, cold, freezing, burns, mechanical irritants, or intracutaneous injections of more than 300 substances.

This condition seems to be a clinical entity and for it the name urticaria calorica has been suggested.

**Summary of Characteristics of a Case Report of Urticaria Calorica.**—A clear understanding of reflex-like reactions of the first type can be obtained by an analysis of the case just reported. The outstanding characteristics were as follows:

*First.*—That a man became spontaneously so sensitive to heat that the slightest exposure of the skin to heat or the heat generated by a little physical exercise or even by mental excitement would give rise to a generalized urticarial rash within a few seconds. The rash in this case was caused specifically and solely by heat. It was estimated that the generation of one calorie of heat by exercise was sufficient to cause reaction if the patient was warmly clad.

*Second.*—The rash spread rapidly, involving almost the entire body within a few seconds. The local reaction at the site of appli-

cation of heat was not much greater than the reaction that occurred generally.

*Third.*—The reaction could be prevented or stopped by the application of cold of any source. This included the application of ice, cold water, or even cold air to the skin and even the ingestion of cold water.

*Fourth.*—Sensitiveness to heat was greatest when body temperature was the lowest. When the body temperature was 94° to 96° reactions were easy to elicit; when it approached normal, reactions were mild and difficult to elicit.

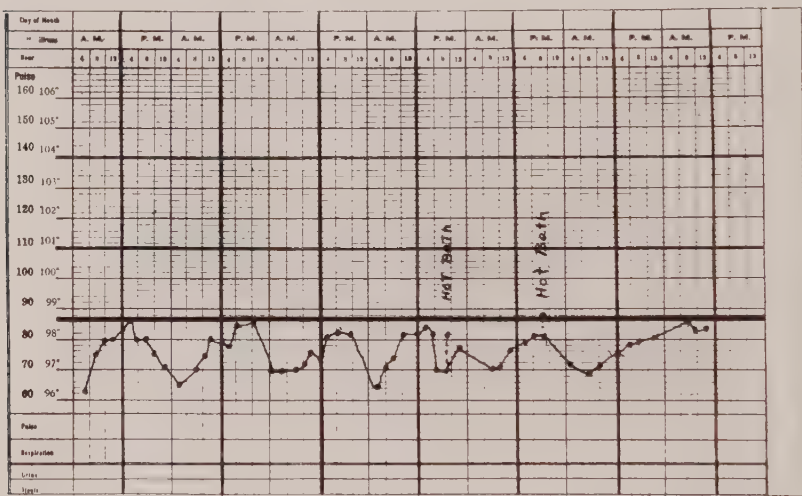


Chart III.—Typical temperature chart of a heat sensitive case—that is, a variable temperature frequently reaching markedly subnormal. In two such patients a morning temperature of 94° F. was not uncommon with an afternoon temperature frequently not exceeding 97° F. Reactions in cases which react promptly occur with a rise in temperature. In cases of delayed reaction, symptoms sometimes occur one hour or more after the rise in temperature. Note the marked temporary rise coincident with a hot bath. Marked relief usually occurs coincident with greater constancy of body temperature especially if it remains nearly normal.

*Fifth.*—The reaction was not followed by temporary exhaustion of the skin except in the following respect: A number of reactions could be produced within a short period of time (twenty-five in twelve hours or less). However, each reaction would be associated with a rise in temperature. When a reaction was produced at a given temperature, a second reaction could not be produced unless the heat applied was sufficient to raise the body temperature

at least 0.2 degree higher, and after the body temperature had been raised to normal or a little above, further reaction was very difficult to elicit during the ensuing twelve hours, even after the temperature had dropped again. The peculiarity of reacting to heat at a given body temperature was partly exhausted by reaction at that temperature.

*Sixth.*—Tolerance for heat was not increased by frequent exposure to heat except in the following respect. If frequent exposures to heat raised body temperature until it approached normal, further reaction was difficult to elicit.

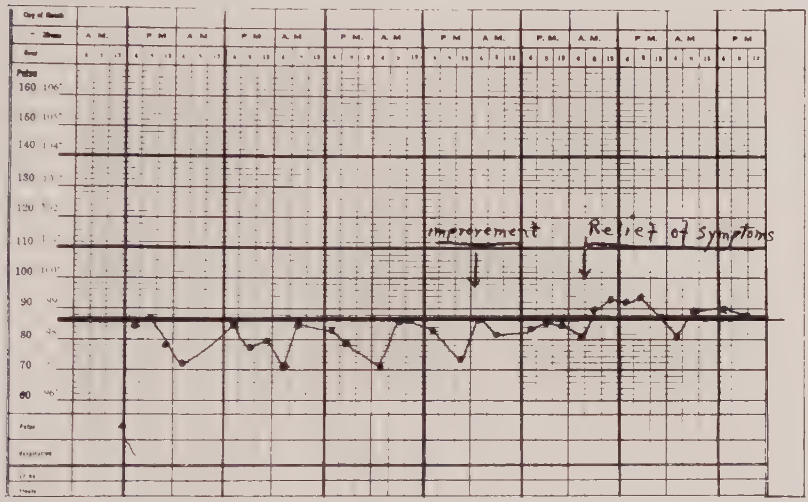


Chart IV.—Temperature record of typical heat sensitive case. Symptoms were marked during the days in which the temperature fell to 97° F. Relief occurred almost immediately when the temperature, after the use of a therapeutic measure, began to range around normal. This patient, though heat sensitive, reacted only in cold weather. His symptoms would always follow exposure to cold but would not appear until he was subsequently exposed to heat. In other words, symptoms, after a drive in a cold wind, would not appear until after he entered a warm room or exercised.

*Seventh.*—Slight eosinophilia followed reaction.

*Eighth.*—Reaction could be prevented by the administration of one-half c.c. of adrenalin subcutaneously.

*Ninth.*—The degree of sensitiveness varied from time to time and diminished markedly during the summer months.

*Tenth.*—It appeared likely that the impulse responsible for reaction was transmitted through the medium of the nervous system, since it spread promptly from the arm when exposed to heat, even

when a tourniquet was applied so tightly around the arm above the the exposure that neither blood nor lymph could enter or leave the arm except through anastomoses with vessels in the bone marrow.

**Comments upon Reactions of the First Type.**—Whereas the case of urticaria as above reported is a classical example of sensitiveness to heat, it is by no means the type of case usually observed. The patient's sensitiveness was much more intense than usual and reactions occurred more promptly. As a rule, more heat is required to produce reaction and reactions ordinarily occur after a period of a minute or so rather than after a few seconds. Furthermore, symptoms usually involve tissues other than the skin and cannot be observed so easily.

The history and clinical findings in heat sensitive cases of this type are rather characteristic. Sensitiveness may apparently start at almost any age, but usually occurs after the age of forty. It rather frequently follows an acute infectious disease, such as pneumonia. The most common symptoms are nasal reaction, bronchial asthma, urticaria, or angioneurotic edema which can be brought out specifically by exposure of the skin to heat and almost invariably by the heat generated under the influence of mental or physical exertion. Most patients in whom allergic symptoms are brought out by emotional disturbances, crying, laughing, excitement, nervousness, physical exertion, or by heat, fall into this group.

Reaction in heat sensitive cases is usually at its maximum during the winter months and in changeable weather, especially when the nights are cold. Many patients become symptom free in warm weather. Reaction is usually at its worst at midnight or in the early morning hours when the temperature of the air is lowest and when body temperature is subnormal. Frequently a patient is symptom free at other times during the day. Some patients are prone to react during the first cold days of the fall months and are at other times, relatively free from attacks. One patient became symptom free during the febrile period of an infectious disease. These peculiar characteristics can be accounted for, I believe, by the fact that such patients are likely to be most sensitive when their body temperature is lowest—reaction being prone to occur during the period at which temperature rises from subnormal to normal. All cases are not alike in this respect, however. A few

react most markedly in hot weather and during the hottest part of the day.

Several cases were markedly relieved through the avoidance of exposure to cold and several by the appropriate application of heat —that is, by hot baths, exercise, etc., given at a time (6 and 10 P.M.) when temperatures were nearly normal and for the purpose of preventing, if possible, a marked fall to subnormal.

**Heat Sensitiveness of a Second Type.**—Heat sensitiveness of the second variety differs from that of the first in that a local increase in temperature in certain tissues is more effective in producing reaction than is a general increase in body heat.

CASE 31.—*Heat Sensitiveness of a Second Type.*—The patient, age thirty, gave a history of autumnal hay fever for a period of three years. She would experience some relief at the time of the first frost, but would continue to have nasal reaction characterized by swelling of the mucous membrane of nose, sneezing, and rather profuse secretion off and on during the entire winter. The history was otherwise negative.

*Physical Examination* made in December showed nothing of importance except a pale swelling of the mucous membrane of the nose with increased clear mucous secretion.

*Sensitization Tests* were positive only for the ragweed pollen group.

*Laboratory Examinations.*—Negative.

*X-ray Examinations.*—Negative except for two dead teeth.

*Physical Tests.*—A hot compress applied to the nose caused a complete obstruction of the air passages within three minutes. Ice applied to the chest at this time had practically no effect. Ice applied to the nose caused almost immediate shrinking of the nasal membrane so that the patient could breathe freely through the nose. The simultaneous application of heat to the nose with ice to the chest did not cause obstruction of the nose so quickly as did the application of heat alone. Heat to the body combined with physical exercise had little effect upon the condition of the nasal mucous membrane, but a little heat applied to the nose subsequently caused the membranes to swell almost immediately.

**Variations in Reactions of the First and Second Types with Brief Case Reports.**—Reactions in each of these types vary in the fact that some react to heat most markedly if they are exposed to cold before they are exposed to heat. It does not seem advisable to separate this class widely from the others for in each variety a change in temperature seems more effective in producing reaction than a constant temperature of any specific grade. However, in many cases change in temperature from cold to heat dominates the pic-

ture—in fact, so much so that the patient's story is often very misleading. They complain of reaction caused by cold rather than by heat. In one case, for example, the patient gave a history of having urticaria each year during the first cold days of the fall months. He claimed that his illness was caused by severe chilling. Examination and a more careful history, however, showed that his outbreaks occurred only upon exposure to heat but that he was sensitive to heat only after a marked exposure to cold. In another case of the sort, a woman gave a history of asthma occurring only when she was exposed to cold. When tested with ice rubs and refrigerated air, however, she did not respond with either cough or shortness of breath. When she was subsequently exposed to normal or warm temperatures, however, she would react immediately with an attack of asthma.

**Combined Sensitiveness.**—The above cases of sensitiveness to the action of heat stand in marked contrast to the ones of combined sensitiveness to be reported subsequently. In combined cases, the local action of heat may be greatly accelerated and greatly exaggerated by the effect of cold in other localities—in fact, so much so that the patient may actually react most frequently upon exposure to cold. Vice versa, the local effect of cold may be greatly accelerated by the simultaneous action of heat in other localities or by exercise—in fact, so much so that the patient may react to cold only when overheated.

The following case is interesting in that nasal reaction caused by heat was accelerated and exaggerated by the effect of ice upon the skin of the body. The condition could be relieved by the local action of an ice compress upon the nose. Relief could be obtained by the ice compresses much more quickly, however, if the skin of the body was exposed to heat or even if heat was generated internally through the effect of exercise.

CASE 32.—*Combined Sensitiveness.*—The patient, a girl of thirteen, gave a history of spells of sneezing, swelling of the mucous membranes of the nose, and profuse watery secretion which had started about the age of six and had troubled her off and on almost the entire time since. She noticed that her spells were more severe and more frequent in the winter months, upon cold days, and in changeable weather. She noticed that she would have an attack of sneezing almost always when she was severely exposed to cold and frequently upon such slight exposure as that experienced upon getting up out of bed, upon getting her arms from under the bed clothes, upon taking cold baths, or

when exposed to cold wind. She noticed that she was relieved to a certain extent by warmth.

*Physical Examination* disclosed nothing of importance except pale swelling of the mucous membrane of the nose with considerable clear watery secretion.

*Laboratory Examinations* were negative.

*X-ray Examinations* were negative.

*Sensitization Tests* were negative.

*Physical Tests.*—When she was tested in a refrigerator at 36° F, she experienced no change in her symptoms except possibly a little relief. An ice rub to the skin caused no reaction. A hot compress applied to the nose caused the membranes to swell within a few minutes. The application of an ice compress to the nose gave her relief within a few minutes. The simultaneous application of a hot compress to the nose with an ice rub to the skin of the body caused the nose to stop up completely within a few seconds. This observation was verified several times. Reaction produced by the simultaneous application of heat and cold was found to be more severe and to occur more quickly than that which followed the application of heat alone. If ice were applied to the nose and simultaneously heat to the body, relief was obtained more quickly than through the use of ice alone. Finally, a nasal reaction which had been caused by the local effect of heat in the nose could be relieved to a marked extent by severe physical exercise when the patient was warmly clad.

The following case is reported as a typical example of combined sensitiveness in which the reaction, asthma, was brought on by the effect of cold air upon the bronchial mucous membrane and exaggerated by the simultaneous action of heat upon the skin of the body or by exercise.

CASE 33.—*Combined Sensitiveness.*—The patient, a man of 49, gave a family and past history which was negative or of no interest in this connection.

He gave a history of having had asthma during the winter months for fifteen years, much worse since he had influenza four years ago. His attacks consisted of hoarseness, severe coughing spells, and severe asthma. He had never noticed anything which had influenced his attacks at all except exposure to coal smoke and occasionally exposure to cold air. Attacks were occasionally brought on, he thought, by exercise.

His worst attacks would occur at one o'clock in the morning and last until about four. He would frequently have such attacks for months at a time. Many of the attacks would require adrenalin for relief and often adrenalin combined with morphine.

*Physical Examination* showed a robust, slightly plethoric, individual who showed slight wheezing as he breathed. There was found in addition to this a slightly deviated nasal septum, a slight grade of oral sepsis, scattered mucous râles in the lung on inspiration and expiration, a slight grade of cardiac hypertrophy, a systolic blood pressure of 176 with a diastolic pressure of 120 and tachycardia (the pulse rather varied from 100 to 110).

*Laboratory Examinations* were negative throughout.

*Roentgen-ray Examinations* were negative except for the finding of a moderate grade of cardiac hypertrophy.

*Sensitization Tests* were negative except for slight reactions obtained with some of the hairs. None of the tests gave large reactions with typical pseudopods.

*Physical Tests.*—The patient in my office was subjected to physical exercise, heat applied to the body, ice applied to the body, ice applied to the nose, heat applied to the nose, heat to the chest, and simultaneously ice to the nose, and ice to the chest and simultaneously heat to the nose. All these tests were negaive.

He was put in a refrigerator at 36° F. without noticeable effect of any sort. After he had been in the refrigerator for five minutes he was directed to exercise by stooping over five times during a period of about thirty seconds. At the end of this time, he had a violent attack of coughing and immediately followed by a severe attack of bronchial asthma. Similar exercise occupying a period of over two minutes and at least five times as severe in my office had caused no noticeable symptom. During this attack of asthma, his clothing was removed above the waist and his body thus exposed to cold air. Within thirty seconds his attack of asthma subsided and soon disappeared. An attack was again brought on while in the refrigerator by having him clothe himself and exercise. This was again relieved by the effect of cold air upon the skin.

He was brought to my office symptom-free. While in the office he was caused to inhale cold air from a towel mask containing ice. Expiration was directed to one side of the towel so as not to heat it up. No result followed this. While breathing the iced air again, the heat of a one thousand watt nitrogen lamp was applied to the chest. This brought on a severe attack of coughing, followed by asthma within thirty seconds. It was relieved within thirty seconds by the application of ice over the skin of the chest and arms.

**Comment.**—It is interesting to repeat the fact in this case that asthma could be caused by the application of cold in one locality and relieved by the same element, cold, applied in a different locality and that the action of cold upon the bronchial tree was augmented and accelerated greatly by the effect of heat regardless of its source.

## Cold Sensitiveness

Sensitiveness to cold is less common than sensitiveness to heat. Interesting to relate, symptoms caused by sensitiveness to cold can often be relieved by heat of any sort, including the heat generated by exercise. This even includes the symptom asthma which can be relieved by exercise taken even while the patient is severely asthmatic. It is essential to differentiate between true cold sensitive cases and heat sensitive cases which react to heat only after exposure to cold. The history may seem similar, that is, one of reaction caused by cold. Heat sensitive cases react only during the process of warming up and are made worse instead of better by heat.

It is interesting in this connection to mention a case reported by Wallace in 1909 in which a patient following the ingestion of ice cream and a glass of cold water had an attack of asthma characterized by great difficulty in breathing, profuse watery secretion from the nose and eyes, sneezing, generalized urticaria, cyanosis, and collapse. The patient gave a history of having had similar attacks at various times brought on apparently by the drinking of cold water when overheated. I would not hesitate to guess that these severe symptoms could have been relieved almost immediately by either severe physical exercise, mental excitement or heat.

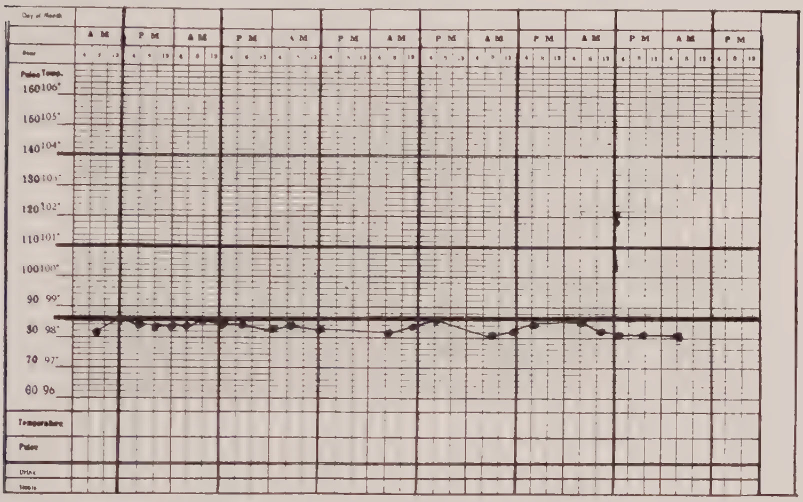


Chart V.—Typical temperature chart in a cold sensitive case—that is, a temperature which ranges around normal or a little above.

The more common symptoms of sensitiveness of cold are coryza, bronchial asthma, and urticaria. I have observed one case in which severe attacks of abdominal pain could be brought on by the ingestion of a cold drink. This could be relieved by the ingestion of hot drinks. Patients with cold sensitiveness probably fall in several clinical groups just as they do in the case of heat sensitiveness. I believe I have observed cases analogous to each of the patients who were sensitive to heat, the only difference being that their reactions were brought on by cold instead of by heat. The temperature in cold sensitive cases is usually about normal or a little above.

The following case was one of asthma as a result of exposure to

cold. Symptoms could be brought on at will by exposure of the skin to cold and could be relieved by either heat or exercise.

CASE 34.—*Asthma Caused by Cold.*—The patient, a woman of sixty-eight, gave a history of asthma and shortness of breath for a period of about four years. She was subject to attacks throughout the entire year, but was much worse in summer than in the winter months. She at one time had been subject to hives.

*Physical Examination* showed an elderly lady who had a marked case of arthritis of the spine, hypertension (blood pressure 208) and cardiac hypertrophy. The mucous membranes of the nose were pale, swollen, and secreting clear mucus. The lungs showed sibilant and sonorous râles throughout. Physical examinations were otherwise unimportant.

*Laboratory Examinations* were negative except for a slight trace of albumin in the urine and low specific gravity.

*Sensitization Tests* were negative except for a moderately positive reaction to orris.

*Temperature* taken over a week's period ranged from $98^2$ to $98^4$.

*Physical Tests.*—The patient was very asthmatic when first observed. She was put under a nitrogen lamp and the chest exposed to its heat for two minutes. At the end of this time she could breathe freely and the lungs were free of râles. Ice was then applied to the chest and within two minutes brought on a severe attack of asthma. Heat was again applied with complete relief. Ice was again applied with recurrence of the asthma. This attack was relieved by having the patient exercise by bending over and touching the floor ten times. An attack was again brought on by the application of ice to the body and was relieved through the use of an autocondensation current for a few minutes.

The blood pressure while she was asthmatic was 208. After a brief treatment with heat, it dropped to 160.

Her temperature taken several times during the period of these tests varied from 98° to $99^2$°.

**Urticaria Caused by Cold After Exposure to Heat.**—The following case is interesting in that the reaction, urticaria, was brought out by cold but only after previous exposure to heat.

CASE 35.—*Urticaria Caused by Cold Augmented by Previous Exposure to the Action of Heat.*—The patient, a man of sixty-three, had been troubled with urticaria and angioneurotic edema for a period of one month. His attacks were worse at night and often came out markedly after exposure to cold, such as after the removal of clothing or after taking a cold bath. The history was otherwise uninteresting except for that of nasal sinus infection which he had had for several years.

*Physical Examination* showed a slight grade of obesity, slight grade of polycythemia, slight grade of cardiac hypertrophy, hypertension (blood pressure 154) Nasal examination showed a deviated nasal septum with swelling of the mucous membranes of the nose and purulent secretion on the left side.

*Laboratory Examinations* were negative.

*X-ray Examinations* negative except for an opaque left frontal sinus and a cloudy right antrum.

*Sensitization Tests* were negative throughout.

*Physical Tests.*—The patient had a few hives when first examined. He was rubbed for a few moments with ice. No results followed this. He was then heated thoroughly through the use of a nitrogen lamp, exercise and an autocondensation current until he was quite hot. His hives were quickly relieved. Ice was then applied to his chest for a moment. A severe general outbreak of hives followed. These were immediately relieved through the further application of heat and exercise.

## Reflex-Like Reactions Caused by Light

Light is a rare cause of reflex-like reaction. I have studied only two cases of the sort. Each complained of the swelling of the mucous membrane of the nose, sneezing, and watery secretion upon exposure of the face to bright light. Upon examination, exposure of the face to light had no appreciable effect. If the patient were caused to look directly at the sun, however, or even at a thousand watt nitrogen lamp, nasal reaction would occur within a few seconds. The effect of violet ray as produced by mercury vapor quartz light was less effective than nitrogen light or sunlight.

## A Description of Reflex-Like Symptoms

As previously mentioned, reflex-like reactions have been observed to cause orbital and nasal symptoms resembling those caused by pollen disease, also bronchial asthma, skin reactions, including erythema, pruritus, urticaria, angioneurotic edema, and eczema, also gastrointestinal upset, eosinophilia, and shock. It seems unnecessary here to describe these reactions in detail. Suffice it to say they resemble those caused by sensitiveness to material agents, such as pollen, animal hair, and foods.

These symptoms fall into three classes, namely, those which occur chiefly at the site of contact; those which occur as a part of a general reaction, and third, solitary reactions.

Solitary reactions are interesting and give rise to marked reaction upon slight exposure. In one patient, for example, the reaction manifested itself chiefly as recurring small papules on the face. In another, as a blotchy erythema on the chest, and in another, by the appearance of discrete hives on the chest which would come out under the influence of heat, physical exercise, or emotional

disturbance. Solitary reactions of this sort occurring on the skin are interesting but not important. If they occurred near the opening in a sinus, in a bronchus or in the ureter or other important structure, however, it would be very important and might cause a profound illness upon very slight provocation. It is believed that many severe illnesses which occur from little or no apparent cause or reason are examples of solitary reactions. (See Fig. 60.)

When reactions occur promptly their interpretation is relatively simple. When they are delayed, however, the interpretation is extremely difficult. In one case, for example, subject to deep urticaria and angioneurotic edema, reactions could be brought out by hot baths but never within a period of less than thirty minutes. In this case, the rash could not be stopped immediately by the application of cold as in the case of immediate reactions. A cold bath taken during the time of the eruption would reduce the itching somewhat but gave the patient a feeling of nervousness which was extremely disagreeable. It would eventually result in a reduction in the size of the wheals. The patient ran almost constantly a subnormal temperature. Through keeping the temperature at a higher level by frequent hot baths and thyroid extract, he was able to avoid the attacks except when subjected to the effect of unusual heat or mental strain.

Reflex-like reactions have the characteristics which follow. They differ from contact and pollen reactions in many respects as can be observed by comparing them with the characteristics of pollen and physical contact reactions mentioned previously.

*First.*—A family history of hay fever, asthma, or hives, can be obtained in about fifty per cent of cases.

*Second.*—The reaction is characterized by erythema, edema, itching, and activity of nonstriated muscle and secreting structures as caused by stimulation of the autonomic nerve mechanism.

*Third.*—Sensitiveness may appear at any age but usually late in life.

*Fourth.*—The condition varies greatly in intensity from time to time. It differs markedly in this respect from contact reactions and from pollen reactions which are remarkably constant from year to year upon a given exposure.

*Fifth.*—The condition does not seem necessarily to be permanent.

*Sixth.*—The skin is not exhausted locally by reaction. In the case of prompt reaction, several can be elicited within a period of one hour.

*Seventh.*—Local tolerance does not necessarily follow frequent exposure to the irritating agent except as influenced by change in body temperature.

*Eighth.*—General tolerance frequently follows repeated exposure to the irritating agent. Apparent tolerance can often be accounted for by a change in body temperature.

*Ninth.*—Symptoms of general or constitutional reaction, such as collapse and eosinophilia, may follow severe exposures in highly sensitive cases.

*Tenth.*—Adrenalin in small doses frequently relieves the reaction in cases that react promptly.

Reflex-like reactions are prone to be seasonal and prone to occur at certain times of day or night and also at irregular intervals upon suitable exposure to the agent responsible for reaction. They are markedly influenced by changes in bodily conditions and body temperature, also by the temperature of outside air, and by the humidity of the air and by sudden weather changes. Asthma caused by sensitiveness of the bronchial mucous membrane to cold, for example, is made worse by dry air because of the cooling of the membranes by evaporation. Patients of this sort are much more comfortable in a moist atmosphere and can be relieved to a marked extent by moist inhalations. In patients, however, in whom the bronchial mucous membrane reacts to heat, the reverse is the case, namely, they are benefited by the inhalation of dry air and made worse by humid air.

It is not uncommon to find the nasal mucous membrane sensitive to local heat. This can be relieved frequently through the inhalation of cold air or by the application of a cold compress to the nose. Such cases are made worse, I am sure, by polyps or mechanical defects in the nose which prevent its proper ventilation and cooling. Such cases may be improved by operations which result in better ventilation.

Patients with thermic sensitiveness not only react abnormally to heat and cold but seem predisposed to acute infectious diseases by thermic changes which have little effect upon normal individuals. Slight weather changes frequently result in severe febrile attacks

ordinarily diagnosed influenza, acute bronchitis, and bronchopneumonia. It is possible that this is simply a result of the mechanical disturbances in the respiratory tract caused by reaction. The fact, however, that these attacks are so severe and frequent leads one to believe that the cause is deeper and that resistance to acute infection is actually reduced. I believe further that of individuals who seem predisposed to infection upon slight exposure to weather conditions, many are subjects of thermic sensitiveness.

### Theoretical Explanation of Reflex-Like Reactions

A theoretical explanation of these remarkable reactions caused by the action of heat or cold or by combined action of the two, is extremely difficult. One might call them simple reflexes. This, it seems to me, would be putting a cloak of knowledge around uncertainty. It might satisfy one for the time being but it seems to me that an adequate explanation needs be more detailed than this. The mechanism involved in reflex-like reactions would seem much more complex than that involved in contact reactions. In the latter condition, the tissues chiefly affected are those which are directly exposed to the irritating agent. In the former case, however, the tissues involved may be distributed over a large part of the entire body.

One might advance the same theories in this connection which were used in an endeavor to account for contact reactions. We might assume that the action of the physical agents in the contact cases was direct upon peripheral tissues or peripheral efferent nerve endings while in the reflex-like cases that the action was exerted upon sensory or afferent nerve terminals. Through the latter abnormal impulses might be generated and transmitted to the autonomic nerve mechanism and there give rise to the explosive impulses which would manifest themselves as reaction.

The underlying condition responsible for reflex-like reactions seems to me to be one of an injured nerve mechanism. One might go further and say that it seems to be a pathologic reaction of the heat regulating mechanism. It seems truly remarkable that warm-blooded animals are able to maintain a constant body temperature under such varying conditions of heat and cold, moisture and dryness of the air, rest and functional activity, as the majority are subjected to. Body temperature is maintained at a constant

level through very complicated reactions which vary the caliber of the surface vessels and vary the secretion of moisture from the skin, nasal and bronchial mucous membranes. When the heat regulating mechanism is normal, body temperature can be maintained at a remarkably constant level under the most varied external and internal conditions. It seems easily within the realm of good reason that this mechanism at times is injured and if injured, might react in an abnormal manner, not only in relation to the dilation or contraction of vessels but also in relation to secretion and activity of nonstriated muscle in general. If such an abnormal mechanism should exist in a person of allergic strain, it seems conceivable that this mechanism might give rise to the peculiar manifestations of allergy which we ordinarily term asthma, allergic coryza, urticaria, angioneurotic edema, etc.

One might advance in support of such a theory the fact that a very large proportion of patients who are subject to reflex-like reaction caused by sensitiveness to temperature change date the onset of their symptoms from a severe illness—often an infectious disease.

Bovie and Klein's experiments are interesting in this connection. They demonstrated that Paramecium caudatum could be so sensitized to heat by exposure for four or five seconds to fluorite rays that a slight rise in temperature in the medium in which they lived (to 17° C.) would cause death almost immediately—in fact, even a rise in temperature to the degree which is most favorable to the reproduction and life of paramecia would prove quickly fatal. If unicellular animals can be sensitized and react upon slight rise in temperature, it is not unreasonable to suppose that the same is true of certain cells in the human body. If cells which were sensitized to heat happened to play important rôles in the physiology of the autonomic nerve mechanism, they might quickly cause profound disturbances under the influence of very slight rises in body temperature.

In a personal communication, Dr. James B. Murphy stated to me recently that he and his assistants, Dr. J. A. Hawkins and Harry Clark, had found that heat sensitized the skin of warm blooded animals to x-ray, and vice versa, that x-ray sensitized the skin of animals to heat so that a burn could be produced by either agency with doses which alone were insufficient to materially affect the skin. If the animals so sensitized to heat happened to have been

human beings of an allergic strain, it is not inconceivable that they might have reacted in an unusual way and that the symptoms might have resembled those of overactivity of the autonomic nerve mechanism which we recognize in human beings as erythema, pruritus, or urticaria.

Preliminary experiments have been performed by the writer in which an effort was made to sensitize animals to heat by injuring them. These experiments are incomplete and only the briefest account of them can be given. The animals chosen were young growing frogs and minnows. A considerable number were given a half erythema dose of x-ray and some three to five days later were subjected to change in temperature. Unfortunately, the majority of both frogs and minnows were killed by placing them in water which was too warm, namely, at temperatures between 42° and 48° C. It was found, however, that normal frogs and normal minnows could tolerate a rise in temperature to 38° C., whereas if the x-rayed frogs were subjected to a sudden change from room temperature to 38° C. they would die immediately. The x-rayed minnows were not so active as normal minnows to begin with, were very quiet and many were swimming on their backs at a temperature of 30° C. None survived a temperature exceeding 35° C. Normal minnows seemed quite lively and well at a temperature of 35° C.

No conclusion concerning the specific effect of x-ray can be made from these experiments. The conclusion can be drawn, however, that normal frogs and minnows can stand a greater rise in temperature than frogs and minnows which have been injured. If the x-rayed animals happened to have been human beings of allergic strain, it is not inconceivable that the reaction might have been one of overstimulation of the autonomic nerve mechanism and that the symptoms produced might have resembled some of those described in human beings.

Regardless of what the mechanism of reaction may be, certain it is that physical agents can cause symptoms which are remarkably similar to those caused by material substances and most certainly have to be taken into account by physicians who treat them.

### Diagnosis

The diagnosis of reaction caused by heat, cold, or light is relatively simple if reactions are prompt and outspoken and especially

if surface tissues are involved. Diagnosis in the case of delayed reaction is difficult and uncertain and can be made only by comparing symptoms with those of cases which react promptly.

A history of reaction which tends to occur with weather changes, upon exposure to heat or cold, or with variation in the moisture of the air, or upon physical exertion or emotional disturbances should always suggest the possibility of thermic sensitiveness.

An objective diagnosis can often be made in cases which react promptly by exposing the patient to heat or cold or to the simultaneous effect of the two. The method of exposure which is most likely to give a positive result varies with the case. Individuals differ greatly in this respect. One case may fail completely to react upon exposure which induces prompt reaction in others. History often serves as a guide as to the most appropriate method for the application of heat or cold. For example, if a patient gives a history of asthma upon exercise in cold weather, a positive reaction can usually be obtained by testing with cold air by inhalation combined with heat applied to the skin, or exercise.

Satisfactory tests can be made in the majority of cases with the aid of a one thousand watt nitrogen lamp by which heat can be applied to the chest and body, by ice rubs, and by hot and cold compresses. It is a great help in some cases to have in addition to the above a dry cold refrigerator and a steam room. It is important during any of the above tests to have the patient exercise vigorously. It is also important to watch the patient after the tests are made since frequently the change from heat to cold or vice versa brings out symptoms rather than constant exposure of the patient to either agent. It is important to bear in mind also that in testing with cold air and warm air more cooling of the bronchial membranes can be obtained by the inhalation of dry air than by cold moist air and, vice versa, more warmth can be applied through the inhalation of damp air than by warm dry air.

A temperature chart taken over a period of several days is important in thermic cases, especially in heat sensitive cases since many of the latter are inclined to react only when the temperature is markedly subnormal.

As previously mentioned, reactions upon exposure to temperature change may be very marked in highly sensitive cases and even result in severe febrile attacks. Undue exposure should be avoided.

## Treatment

Patients with thermic sensitiveness can be treated along several different lines.

*First.*—By avoidance of specific cause of illness.

*Second.*—By avoidance of contributory causes.

*Third.*—By specific treatment.

*Fourth.*—By symptomatic treatment.

1. **Avoidance of Specific Cause** depends upon a careful study of a case. It is necessary to know which tissues are sensitive to heat and which to cold before advice can be given as to avoidance of either for in combined cases, heat in one locality may cause reaction and applied in another locality may actually relieve it. In heat sensitive cases reaction can often be avoided by such simple procedures as avoidance of undue exercise, mental excitement, avoidance of the wearing of excessive amounts of clothing, by the use of fans, and by so simple a procedure at times as wetting the hands. Patients who are highly sensitive and who might be inclined to react as many as twenty-five times can actually keep themselves relatively comfortable by the careful avoidance of undue quantities of heat. Cold sensitive cases can frequently relieve themselves by exercise. This, however, is not true in combined sensitiveness. In this case, exercise frequently makes symptoms worse.

Patients with thermic sensitiveness are frequently benefited by change in geographic environment. This can be attributed to not only the lesser extremes in change of temperature but also to differences in humidity. Patients whose tissues react locally to cold do better in a moist than in a dry atmosphere because of the lack of cooling by evaporation. Vice versa, patients whose tissues react locally to heat do better in a dry atmosphere than in a moist one. These facts can be taken advantage of in therapy and should always be taken into consideration when choosing a climate for a highly sensitive individual.

Thermic cases should be cautioned against undue exposure to weather changes. Undue exposure to either heat or cold often results not only in reaction but in a serious febrile illness.

Heat sensitive cases frequently run a markedly subnormal temperature and react most markedly when the temperature is lowest. Such cases can be treated best by avoidance of the low temperature. In several instances, attacks which were prone to occur at midnight

and last until morning were prevented or delayed greatly in their time of appearance through the use of a hot bath and exercise at six P.M. and nine P.M. given for the purpose of producing heat and preventing thereby the unusually low early morning temperature. Such cases in several instances have been benefited somewhat by thyroid extract and insulin and also through the use of non-specific vaccine therapy. In each instance, it was believed that the improvement noticed was a result of the higher general average of body temperature.

2. **Avoidance of Contributary Causes.**—It is not necessary to repeat here the paragraphs of Part I written on this subject in connection with sensitiveness to material agents. Many abnormal body conditions have an effect upon heat reactions and if such are corrected, the patient may improve. In one hive case, for example, who was sensitive to heat, reaction was completely relieved by a hemorrhoid operation.

3. **Specific Treatment.**—Tolerance, in a measure, can be gained through frequent application of the agents which cause reaction. This is more easily accomplished in cold sensitive cases than in heat sensitive cases. A number of patients have been relieved in marked degree through the frequent use of hot baths or cold baths or one followed by the other. This is usually associated with a feeling of well being and an improvement in general health.

4. **Symptomatic Treatment.**--Adrenalin, atropine, and sedatives have the same effect in this type of illness as in patients sensitive to material substances and can be used according to the routine mentioned in this connection in Part I.

## CHAPTER XX

## COOPERATION BETWEEN PATIENT AND PHYSICIAN

A serious obstacle which often stands in the way of success in the treatment of chronic allergy is the mental attitude of the patient. This attitude is one of skepticism and unwillingness to cooperate fully for an extended period of time. I know of few illnesses in which the patients, as a class, are so hard to handle. Patients with tuberculosis, diabetes, heart disease, or even with carcinoma will usually go the limit in an effort to get well if the essentials of treatment are explained to them. This is not often true of patients with chronic allergy. It is believed that this attitude is not a specific result of the disease, allergy, but rather the result of a long illness of a type which rarely terminates fatally, which is subject to frequent change for better or for worse without apparent reason, and for which many remedies have been advertized as cures. Few disorders can become so chronic as allergy—it can last from childhood to old age—few disorders are subject to such rapid and apparently unexplainable change, and finally, there are few disorders for which so many remedies have been advertized as cures.

Many patients are persuaded to try one remedy after another—usually remedies recommended to them highly by their friends or neighbors as sure cures. They experience so many disappointments that they are eventually unwilling to make a serious effort along any lines which requires time, effort, or sacrifice. This is unfortunate for there are few illnesses which require more care, study, and time both in diagnosis and in treatment than chronic allergy.

Unfortunately, the mental attitude which characterizes many patients characterizes also many physicians; however, not necessarily the physician's attitude toward allergy, but rather his attitude toward the relief of any chronic disease which he knows by experience resists the remedies which are usually recommended and which often improves spontaneously without apparent cause. They rightfully question the effect of a method of treatment for a disease which often gets better without treatment. The majority of physicians have tried many remedies which have been highly recom-

mended by physicians of unquestionable ability and honesty and have had so many disappointments that they are inclined to disbelieve enthusiastic statements concerning the possibility of its relief. This is unfortunate for many patients who are under treatment are persuaded to stop by a casual remark of some physician of their acquaintance.

For the above reasons, it is almost necessary at the commencement of the study and treatment of a chronic case to explain to

Fig. 75.—Case of perennial asthma of six years' duration caused among other things by combined sensitiveness to heat and cold. An attack could be brought on by the breathing of warm or moist air if his body were at the same time exposed to cold. Some improvement followed a change to a dry climate where evaporation cooled the bronchial tubes but had a less marked chilling effect upon the skin than moist air. He was unable even in a dry climate to attend to his business affairs. Upon common sense measures directed toward the avoidance of undue exposure of the body to cold and the bronchial tubes to warm air and upon therapy with frequent cold baths given for the purpose of gradually increasing tolerance for cold, marked improvement occurred even in a damp cold atmosphere. Note the ill fit of his carefully tailored vest. The evident subsidence in the size of his chest followed clinical relief of one week's duration. He cannot now voluntarily assume a position which will cause his vest to fit properly. Improvement to this degree does not assure one of a patient's cooperation in the face of a recurrence of symptoms.

the patient the reasons for this state of affairs. They should be acquainted with the fact that the causes of allergy are multitudinous, that a substance which is injurious to one individual is harmless to another, that a change in climate or environment which is

beneficial to one may be ineffective or actually injurious to another, that remedies in general which benefit one may fail completely in a majority of others—all because the cause of the illness is varied.

At the outset it should also be explained that should the illness be relieved while following out a certain theory and later recur, the theory under which relief was obtained should not necessarily be discarded, and that above all, the patient should not be persuaded to try at random other remedies which may have helped some friend. Instead, the cause of the recurrence should be sought and an effort made to combat it.

Finally, it must be mentioned for the sake of the subject under discussion, for the sake of the patient, and for the sake of the physician, that a thorough study of the essentials of this line of work should be made before physicians take it up. Otherwise, disappointment is almost certain. Nothing could be more erroneous than a view widely held that a case can be diagnosed through the use of a few skin tests and that cure can be obtained by inoculating the patient with materials which give positive tests. This line of reasoning may be correct in a certain number of pollen sensitive cases. It is incorrect, however, if applied to the great majority of cases, especially perennial cases. Methods of diagnosis and treatment which have been recommended in good faith and which have been made as nearly fool proof as it is possible to make them are destined to fail in the great majority of cases unless combined with thorough study of the individual, for in this, more than in almost any other disease, methods of diagnosis and methods of treatment have to be modified to suit the individual. A method which succeeds well in one individual may completely fail in another who apparently is suffering from the same illness.

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# INDEX

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